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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

MARCH, 1935

ORIGINAL ARTICLES.

THE CLINICAL VALUE OF ALTERNATE SUCTION AND PRESSURE IN THE TREATMENT OF ADVANCED PERIPHERAL VASCULAR DISEASE.

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From the therapeutic standpoint patients with peripheral vascular disease can be divided into two groups: (*a*) Those whose symptoms are due to simple spasm with no, or very slight, organic vascular obstruction; and (*b*) those whose symptoms are due primarily to advanced organic disease of the arteries. The symptoms of the first group can usually be alleviated by producing vasodilatation with drugs, diathermy, contrast baths, local heat in the form of the warm cradle, or finally with sympathetic ganglionectomy. The efficacy of these therapeutic procedures depends upon local dilatation of the peripheral bloodvessels.

In the later stages of peripheral vascular disease the walls of the arteries become thickened and more or less rigid. They have not only abnormally small lumina, but are also unable to dilate even when vasoconstrictor tone is abolished by nerve block or by sympathetic ganglionectomy. Under these conditions the therapeutic procedures mentioned above are much less likely to increase blood flow, and they usually fail to improve the nutrition of the tissues (Adson and Brown;[1] Morton and Scott[2]). Eventually most patients with

* Aided by a grant from the Philadelphia Heart Association.

† Aided by a grant from the Committee on Scientific Research of the American Medical Association.

advanced organic disease of the arteries suffer from trophic changes, ulceration and gangrene, leading finally to amputation. They often present a difficult therapeutic problem to both the clinician and the surgeon.

Landis and Gibbon[3,4] found that the digital skin temperatures of the lower extremities of patients with advanced organic vascular occlusion could be elevated by applying alternate suction and pressure to the affected extremity. Preliminary studies indicated that to increase blood flow most efficiently it was advisable to have: (1) Relatively brief periods of suction; (2) brief periods of pressure; and (3) diminished vasoconstrictor tone. Landis[5] observed that this procedure relieved to some extent the clinical manifestations of the ischemia which accompanies organic vascular occlusion.

This paper describes the results of treating a series of patients by means of alternate suction and pressure, with particular reference to the limitations and the possible usefulness of this procedure in the therapy of peripheral vascular disease.

A conservative general estimate of the clinical results so far bears out the encouraging experimental findings in that: (1) The rest pain of ischemia was relieved, at least temporarily; (2) intermittent claudication, when present, became less intense and did not appear so soon in the course of exercise; and (3) indolent ulcers or superficial gangrene often healed in a manner not observed with the usual modes of treatment. Changes in skin color could not be measured quantitatively, but various observers agreed that cyanosis often diminished and that skin color approached normal during the progress of treatment.

I. Selection of Patients and Methods Used. Suction and pressure was applied to the extremities of 29 patients suffering from advanced peripheral vascular disease with pain and ulceration. These patients had shown little progress under the usual conservative treatments, including local warm applications, the warm cradle, antiseptics, vasodilator drugs, or even nerve section. An excessively long period of hospitalization or mutilating surgery seemed to be the only alternative. Those treated in the Philadelphia General Hospital were chiefly diabetics from the metabolic wards, while most of the patients treated in the University of Pennsylvania Hospital suffered from arteriosclerosis, or thromboangiitis obliterans.

The grade of organic occlusion was tested whenever possible by the method of Landis and Gibbon;[6] abnormal findings were checked when necessary by peripheral nerve block (Scott and Morton[7]). In some instances the vasodilator response was tested at intervals during the use of suction and pressure therapy to study objective changes in the circulation of the extremity under observation.

The apparatus used for treating patients in both hospitals was the same as that described by Landis and Gibbon[4] and Landis.[5] During treatment the patients sat or reclined in bed. The affected

extremity was inserted into the aluminum chamber and lay in the horizontal plane upon a pillow in the bottom of the chamber. The extremity could be inspected through the glass top of the box to detect changes in skin color occurring during treatment. The thigh, protected when necessary by a layer of gauze bandage, was encircled at a point 6 inches above the knee by a rubber cuff with two leaves, one sealing during pressure, the other sealing during suction. A layer of adhesive tape was applied to each cuff to keep the rubber in close contact with the skin.

Since the effect of suction and pressure on skin temperature had already been studied in patients with peripheral vascular disease (Landis[5]), no effort was made to control the temperature of the air surrounding the limb in the chamber. The air compressor became warm after running some minutes; consequently the air temperature in the aluminum chamber rose gradually to between 25° and 29° C. One forearm was encircled by an electric heating pad to reduce reflexly the vasoconstrictor tone in the lower extremities so that an adequate reservoir might be available for accommodating arterial blood drawn into the peripheral vessels during suction. The patients usually perspired slightly during the period of treatment.

Suction amounting to between 80 and 120 mm.Hg (*i. e.*, below atmospheric pressure) was applied for 25 seconds alternately with pressure of 60 to 80 mm.Hg (*i. e.*, above atmospheric pressure) for 5 seconds. The time required to change the air pressure within the aluminum chamber from −120 to +80 mm.Hg was reduced to about 3 seconds in order that as little time as possible should be lost in changing from suction to pressure. The time relations of the pressure variations have already been shown diagrammatically (Landis;[5] Fig. 6). Unless otherwise mentioned, −120 and +80 mm.Hg were used for 25 and 5 seconds, respectively. Until patients became familiar with the apparatus it was usually expedient to use −80 and +60 mm.Hg for 25 and 5 seconds, respectively. In a few instances, −150 and +100 mm.Hg were used for 50 and 10 seconds, respectively, without discomfort or injury.

In general when rest pain was severe, or when ulcers had not yet begun to heal, the affected extremities were exposed to suction and pressure for 2 hours, twice daily. If rest pain was very severe, treatment was given even more frequently, and over longer periods. Occasionally for severe nocturnal rest pain, suction and pressure therapy was used at night for as long as 6 hours continuously. After rest pain had diminished somewhat and after ulcers had begun to heal, the duration of treatment was reduced to 1 or 2 hours, at first once daily, then 3 times weekly and finally to 2 hours once weekly.

Ulcers were dressed daily with vaselin gauze; antiseptics were used only rarely, since even the mildest appeared to delay the growth

of granulation tissue and epithelium in ischemic extremities. Parts involved in dry gangrene were merely covered with sterile gauze. Nearly all patients had been treated by means of the warm cradle for days or weeks before suction and pressure therapy was used; the use of the warm cradle was continued during the intervals between suction and pressure treatments.

II. Clinical Observations. Observations on the treatment of 29 patients have been arranged in a series of tables, grouped according to clinical diagnosis. The patency of the peripheral vessels is described under the heading, Vasodilator Response, by recording the maximum skin temperature reached during vasodilatation if a measurable rise occurred. The notation 0 indicates that skin temperature continued to fall, or did not rise at all during the period when vasoconstrictor tone was abolished. The total duration of treatment is given in terms of the number of hours during which the extremity was actually exposed to suction and pressure. The left and right portions of each table describe the status of the patient before and after the application of pressure variations, respectively. The last column gives a clinical estimate of the usefulness of suction and pressure in each instance. The general results will be considered according to diagnosis.

Results. *A. Diabetes.* A total of 14 diabetic patients were treated, 9 having painful, indolent ulcers or gangrene (Table 1), 5 having rest pain but no ulceration (Table 2). The diabetes was kept adequately under control during treatment. Table 1 indicates the clinical findings and results in the presence of ulceration or gangrene. Six of these patients were referred for treatment of ulcers which had failed to show evidence of healing during periods of 6 weeks to 4 months. Two complete failures were encountered. In 1 instance (Case 1) a large, deep ulceration healed, pain became less but slowly progressing osteomyelitis eventually required amputation of the leg. In the other failure (Case 7), 2 of 3 ulcers healed, pain was relieved temporarily, but a large slough in the floor of the third and most extensive ulcer failed to soften, pain again increased and the leg was amputated.

The remaining 7 patients with ulcers improved conspicuously. Rest pain, originally present in 6 cases, was relieved permanently in 5 and temporarily only in 1. Cyanosis decreased and lesions, previously stationary, healed often with considerable rapidity after suction and pressure therapy was begun. Protocol 1 (Case 3) exemplifies this group. Photographs taken before and after treatment of Cases 2, 3 and 4 are shown in Figs. 1, 2 and 3, respectively.

Table 2 summarizes the results in 5 diabetics without lesions. Rest pain and claudication diminished in 4. Case 14, treated for only 6 hours, showed no improvement but at a later period more adequate treatment was followed by relief from discomfort at rest, though claudication was but slightly affected.

TABLE 1.—DIABETES, ARTERIOSCLEROSIS, WITH ULCER OR GANGRENOUS SLOUGH (9 CASES).

TABLE 1.—DIABETES, ARTERIOSCLEROSIS, WITH ULCER OR GANGRENOUS SLOUGH (9 CASES).

Case, sex and age (yrs.)	Additional diagnoses; duration of lesion.	Before treatment.						Suction-pressure treatment, hrs.	After treatment.							Remarks.
		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.	Result.	
1. M., 54	Early osteomyelitis; ulcer on side of foot. 4 mos.	0	..	++	+++	2.0 (deep)	0	100	0	..	0	++	Small sinus	0	Poor	Ulcer healed; pain controlled; osteomyelitis progressed slowly; amputation of leg.
2. M., 63	Myocardosis, edema; gangrene surface of toe. 6 wks.	0	..	++	+++	1.5	Dry flaque	2½	0	..	0	++	0	0	Good	Lesion stationary for 6 wks. prior to suction-pressure; no recurrence in 6 mos.
3. M., 60	One leg amputated previously; necrotic ulcer. 3 mos.	0	0	0	++	1.5 (deep)	0	40	0	0	0	++	0	0	Good	Extreme occlusion: healing began late; necrotic toe lesion began 6 mos. later.
4. F., 59	Slough on great toe from hot water bag 3 wks.	+++	..	0	+++	1.3	Flaque	37	++	+	0	+	0	0	Good	Healing accelerated.
5. F., 42	Hypertension, varicose veins; pressure necrosis of heel 2 wks.	0	..	++	0	0	Large flaque	23	0	..	0	0	0	0	Good	Indolent lesion; responded only to suction-pressure; varices not affected.
6. F., 47	One toe amputated previously; spontaneous ulcer of toe 2 wks.	++	..	++	*	1.0	0	14	++	..	0	*	0	0	Fair	Pain relieved; injury to leg on ward interrupted treatment; ulcer continued to heal.
7. M., 58	Ulcers, (*a*) under malleolus, (*b*) great toe, (*c*) heel. 2½ mos	0	0	+++	+++	2.3 2.0 0.3	(*a*) deep (*b*) 0 (*c*) 0	62	0	0	0 to ++	++	(*a*) open (*b*) 0 (*c*) 0	(*a*) + (*b*) 0 (*c*) 0	Poor	Temporary relief of pain; healing of 2 ulcers; persistent slough required amputation.
8. M., 78	Previous amputation of rt. leg; ulcers, (*a*) toe; (*b*) interdigital space. 4 mos.	0	0	++	++++	1.4 1.0	(*a*) + (*b*) 0	37	0	0	0	0	0	0	Good	Ulceration, previously enlarging, healed completely.
9. M. 62	Indolent ulceration of great toe	++	-6.1 °C.	0	++	1.5	0	20	++	..	0	+	0.5	0	Good	Incomplete; patient died at home of intercurrent pneumonia.

++++ to 0 = degree of intensity of symptom or sign.
* Negress.

TABLE 2.—DIABETES, ARTERIOSCLEROSIS, WITH REST PAIN AND CLAUDICATION BUT NO LESION (5 CASES).

Case, sex and age (yrs.)	Additional diagnoses; duration of symptoms.	Before treatment					Suction-pressure treatment, hrs.	After treatment						Remarks.
		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.	Result.	
10. M., 64	Mild osteoarthritis; rest pain and intermittent claudication. 2 yrs.	0	..	+ +	50	+ + +	18	0	31° C	0	300	+ + +	Good	Relief of pain; no objective changes.
11. M., 57	Arterial occlusion; secondary anemia. 1 yr.	0	0	+	100	+	14	0	0	0	630	+	Good	Relief of pain; claudication delayed; no objective changes.
12. F., 68	Sudden thrombosis; constant pain. 2 wks.	0	..	+ + +	..	Rubor + + +	12	0	..	0	..	Rubor + +	Good	Relief of pain; foot warmer; color less intense; reëntered with gangrene of toe 4 mos. later.
13. M., 55	Alcoholism; thrombosis of partly occluded artery; pain. 4 wks.	0	..	+ + +	..	+	16	0	..	0	..	0	Good	Relief of pain; tided over stage of acute ischemia.
14. F., 67	Cramps at night; claudication	0	0	+ +	50	+ +	6	0	..	+	50	+ +	Poor	Treatment period brief; cramps relieved; claudication unaffected.

B. Thromboangiitis Obliterans. Eight patients with thromboangiitis obliterans (Table 3) were treated for between 5 and 81 hours on account of ulceration accompanied by rest pain (7 cases) and claudication (4 cases). Two patients (Cases 20 and 21) suffered from ulcers which had persisted some months after nerve section. The general results were excellent in 4 instances, good in 1 and fair in 2. Ulcers healed, cyanosis became less, rest pain gradually disappeared and the severity of intermittent claudication was diminished.

Case 17 (see Proctocol), though recorded as a failure, should probably not be thus classified. This patient entered the hospital with a massive gangrenous slough extending to the middle of the right palm, following amputation of the index finger at another hospital. Conservative treatment was out of the question but the patient refused operation until several days after admission. During this period the effects of suction and pressure therapy on severe rest pain were observed with the temporary relief indicated in Protocol 2. The patient finally permitted amputation above the elbow.

Case 18 suffered from dry gangrene of the tip of one toe with severe rest pain. Relief of pain, though striking, was only temporary and the toe was amputated at its base. The patient returned several weeks after operation with renewed pain; suction and pressure therapy was used to aid healing of an indolent ulcer which had persisted at the site of amputation.

Three patients with thromboangiitis obliterans but with no ulceration (Table 4) were treated, 1 for rest pain and 2 for intermittent claudication. Rest pain disappeared, intermittent claudication became less intense and did not appear so soon in the course of exercise.

C. Arteriosclerosis. Three patients hospitalized for lesions associated with arteriosclerosis of advanced grade were treated, with failure in 1 instance and with excellent results in 2. The patient in whom amputation was eventually necessary presented dry gangrene of the toe with excruciating rest pain. Suction and pressure therapy was used for a total of 2 hours over short periods. Rest pain was absent during the use of suction and pressure but returned during the intervals between treatments. The associated polycythemia and varicose veins made permanent benefit very unlikely so that amputation was resorted to without further trial of suction and pressure therapy. Case 28 complained of severe pain which was relieved on several occasions within a few minutes after suction and pressure therapy was started. The ulcers in this patient had previously been enlarging but began to heal quite promptly and closed completely after 91 hours of therapy.

One patient (Case 29; see Protocol) presented on admission marked slaty cyanosis of the great toe with excruciating pain controlled only partially by opiates in moderate dosage. Amputation

TABLE 3.—THROMBOANGIITIS OBLITERANS WITH REST PAIN AND ULCERATION (8 CASES).

Case, sex and age (yrs.)	Additional diagnoses; duration of lesion.	Before treatment.							Suction-pressure treatment. hrs.	After treatment.							Result.	Remarks.
		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		Palpable arterial pulse.	Vasodilator response.	Pain.	Claudication, yds.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		
15. M., 26	Ulcer of toe. 9 wks.	0	30.5° C. (slow)	+ + +	300	0	2.2	0	35	0	...	0	0	0	0	0	Good	Complete relief of constant pain; probably aided by hypertonic saline solution intravenously.
16. M., 30	Amputations; large ulcer dorsum of foot. 5 mos.	0	...	+ +	..	+ + + +	5.6	0	14	0	...	+	..	+ +	3.2	0	Fair	Incomplete; patient left hospital against advice.
17. M., 53	Multiple amputations previously; gangrenous sloughing ulcer of hand; osteomyelitis	0*	0	+ + + +	..	+ + + +	6.0	+ + + +	5	0	...	0 (in pump) + + + +	..	+ + + +	6.0	+ + +	Poor	Conservative treatment forced by patient against advice; pain relieved only while in apparatus; amputation of arm.
18. M., 28	Gangrene, tip of 2d toe	0	0	+ + + +	..	+ + + +	0.9	+ + (dry)	11	0	0	0 (in pump) + + + +	..	+ + + +	0.9 +	+ +	Poor	Pain and slow increase in area of gangrene; amputation of toe; see next line.
	(*a*) Indolent ulcer after amputation of 2d toe; (*b*) ulcer below malleolus	0	0	+ + + +	..	+ + + +	(*a*) 1.5 (*b*) 1.0	+ +	81	0	0	0	..	0 to + +	(*a*) 0 (*b*) 0	0	Good	Ulceration, previously painful and indolent, healed; pain relieved.
19. M., 41	Previous amputation rt. 1st toe; indolent ulcer, osteomyelitis of 2d toe	0	28° C. (slow)	+ +	100	+ + + +	0.4	0	14	0	...	0	..	+	0	0	Fair	Osteomyelitis prevented complete closure of ulcer; minute sinus remained; pain and claudication relieved.
20. M., 37	Chronic ulcer, toe, enlarging after nerve section for pain. 5 mos.	0	0	0	30	+ + + +	1.8	+	71	0	0	0	0	0 to +	0	0	Good	Complete healing after all other treatment had failed; amputation advised but refused.
21. M., 48	Chronic ulcer, toe, 5 mos. after nerve section for pain	0	0	0	30	+ + + +	1.0	+ +	60	0	0	+	0	0	0	0	Good	Claudication relieved; ulcer healed after minor recurrence.
22. M., 59	Chronic ulcer, 4th left finger	0*	0	+ + + +	..	+ + +	1.0	+	22	0	31.2° C. (slow)	0 to +	..	0 to +	0	0	Good	Indolent sloughing ulcer, previously treated without result, healed rapidly.

* Radial and ulnar arteries.

TABLE 4.—THROMBOANGIITIS OBLITERANS, WITH REST PAIN, CLAUDICATION, BUT NO LESION (3 CASES).

* Radial and ulnar arteries.

TABLE 4.—THROMBOANGIITIS OBLITERANS, WITH REST PAIN, CLAUDICATION, BUT NO LESION (3 CASES).

Case, sex and age (yrs.).	Before treatment.					Suction-pressure treatment, hrs.	After treatment.					Result.	Remarks.
	Palpable arterial pulse.	Vaso-dilator response.	Pain.	Claudication, yds.	Cyanosis.		Palpable arterial pulse.	Vaso-dilator response.	Pain.	Claudication, yds.	Cyanosis.		
23. M., 46	0	29° C.	++	...	+	24	0	29.5° C.	0	...	+	Good	Subjective relief; previous amputation prevents walking.
24. M., 58	0	24° C.	0	30	0 to ++++	24	0	26.0° C.	0	1000	0 to ++	Good	Typhoid vaccine; diathermy; baths tried previously without effect.
25. M., 43	0	26° C.	0	30	0 to +++	112	0	27.0° C.	0	100	0 to ++	Fair	Diathermy; baking used without effect.

TABLE 5.—ARTERIOSCLEROSIS, WITH REST PAIN, ULCER, OR GANGRENOUS SLOUGH (3 CASES)*; REST PAIN, NO LESION (1 CASE).

Case, sex and age (yrs.).	Additional diagnoses; duration of lesion.	Before treatment.						Suction-pressure treatment, hrs.	After treatment.						Result.	Remarks.
		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		Palpable arterial pulse.	Vasodilator response.	Pain.	Cyanosis.	Diameter of ulcer, cm.	Gangrenous slough.		
26. M., 78	Large active ulcer exposing tendons, side of foot. 2 mos.	0	..	0	+++	3.0	0	15	0	..	0	+	0	0	Good	Gelatin boot for support probably aided healing; boot alone ineffective.
27. M., 60	Polycythemia; hypertension; varicose veins	0	..	++++	++++	0	Plaque	2	0	..	0 (in pump) ++++ (out)	++++	0	Same	Poor	Varicose veins made relief unlikely; amputation of leg.
28. M., 63	Sloughing ulcers (*a*) 2d toe, (*b*) 3d toe	0	0	++++	*	(*a*) 0.9 (*b*) 0.8	(*a*) + (*b*) 0	91	0	..	0	*	(*a*) 0 (*b*) 0	0	Good	Severe pain at night relieved by treatment, with eventual healing of ulcers.
29. M., 65	Myocardosis, angina; agonizing pain. 2 wks	0	0	++++	++++	0	Blebs	46	0	..	0 to +	0 to ++	0	0	Good	Severe rest pain and threatened gangrene relieved during suction-pressure therapy.

* Negro.

seemed hazardous on account of associated myocardial weakness, angina pectoris and generalized arteriosclerosis. Suction and pressure therapy was instituted with the result that pain diminished rapidly and cyanosis disappeared. The patient was discharged free of rest pain. The foot still showed slight cyanosis in the dependent position, but the previous gray dusky cyanosis had disappeared. A summary of this patient's record is given in Protocol 3.

TABLE 6.—GENERAL SUMMARY.

Diagnosis.	Relief of symptoms and signs.			Total.
	None.	Fair.	Good.	
Diabetes:				
With ulceration	2	1	6	9
Without ulceration	1	0	4	5
Thromboangiitis obliterans:				
With ulceration	2	2	5	9*
Without ulceration	0	1	2	3
Arteriosclerosis:				
With ulceration	1	0	2	3
Without ulceration	0	0	1	1
Totals	6†	4	20	30*

* Case 18 was treated before and after amputation of toe. Results have, therefore, been entered in 2 columns.

† Poor results associated with: (*a*) Osteomyelitis in 1 case; (*b*) gangrenous slough in 4 cases; (*c*) very brief period of treatment in 1 case.

D. Effect of Suction and Pressure on the Various Clinical Manifestations of Ischemia. Table 6 summarizes the general results more briefly. In 29 patients treated with suction and pressure, amputation was performed in 5, and 1 patient was not aided by a period of treatment which was too brief to be considered a fair trial. Thus, 6 patients were aided not at all or only temporarily; in none was there evidence of harm arising from the use of suction and pressure. In the 5 patients coming to amputation a massive gangrenous slough was present in 4, and extending osteomyelitis in 1. Attempts to arrest an early osteomyelitis failed completely even though the cutaneous lesion healed except for a sinus kept open by exudate from the infected bone (Table 1, Case 1; Table 3, Case 19). The results indicate also that deep gangrene makes it unlikely that suction and pressure therapy will be of permanent benefit. When gangrene involves more than the superficial tissues, suction and pressure therapy can do little more than reduce pain temporarily, and possibly put the adjacent tissues in better condition to withstand amputation. The history of Case 18 (Table 3) suggests that after amputation of a digit suction and pressure therapy may make it possible in some instances to avoid more extensive mutilation. The less severe manifestations of ischemia—cyanosis, rest pain, intermittent claudication and indolent ulceration—diminished in many patients during the period when suction and pressure therapy was used.

When patients are first treated, changes in skin color may become obvious almost at once, but more often cyanosis is affected only after several hours of treatment. In a few cases, subjective relief was obtained without any clearly demonstrable modification of skin color.

The effect of suction and pressure on cyanosis seems to depend upon the grade of organic vascular obstruction. In a limb which is ischemic by reason of vascular spasm accompanied by moderate organic obstruction, cyanotic digits often become pink during the first few alternations of pressure. On several occasions when Case 25 (Table 4) came in from out-of-doors (temperature, 18° to 15° C.), both lower extremities were extremely cold and the skin of both feet was intensely pale and cyanotic. The left extremity (the more diseased) was placed in the apparatus, while the other remained in room air at the same temperature. Suction and pressure were applied in the usual way. At the end of the first period of suction the foot became deeply red except for the second, third and fourth toes which still remained pale and cyanotic. The second suction period produced redness of the fourth toe and of the bases of the second and third toes. The fourth suction period reddened all the skin of the foot excepting that at the tip of the third toe. One minute later this digit was also normal in color. The other extremity meanwhile remained pale and cyanotic.

When advanced organic obstruction is present (*e. g.*, Case 8, Table 1), digits, originally cyanotic, will gradually become normal in color as blood invades the skin from the base of the digit. The progress of this change in color is very much slower, but it can be followed from day to day and is naturally subject to changes in environmental temperature. The hyperemia which accompanies suction may finally become almost as pronounced as in normal skin. The color changes are often striking enough to be noticed spontaneously by the patients themselves. Normal skin color, once induced, usually persists even during the winter months.

Those areas of skin which are actually necrotic exhibit no change in color. Presumably local asphyxia has produced thrombosis and stasis, closing the vessels permanently so that blood flow cannot be resumed even with external physical aid.

Lewis *et al.*[8] produced pain in normal subjects by exercise while blood flow was restricted. Restoration of blood flow quickly relieved this pain. Since suction and pressure therapy increases blood flow, as indicated by elevation of skin temperature, it should also alleviate rest pain in a relatively short time. The immediate effects on rest pain have been described (Landis[5]) and are illustrated in Protocol 2. In the many hours during which suction and pressure have been used, rest pain has been in general strikingly relieved during the period of treatment. This relief proved to be only

temporary when massive gangrene or large gangrenous sloughs were present. The pain of neuritis was not affected.

Patients with indolent or slowly enlarging ulcers, but without frank gangrene, large sloughs or extending necrosis, obtained more lasting relief from rest pain. As a rule, patients exhausted by continued pain fall asleep while the extremity is in the apparatus. Sleep ordinarily became possible without sedatives after a few days.

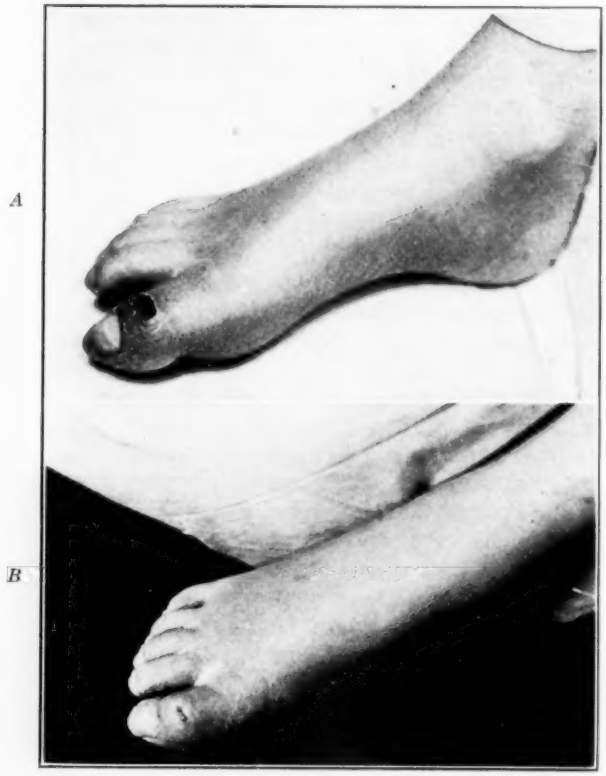

FIG. 1.—Patient R. S., Table 1, No. 2, showing lesion: (*A*) After ordinary conservative therapy for 6 weeks; and (*B*) after suction and pressure therapy, totaling 24 hours in 3 weeks.

Discomfort may arise during treatment if ulcers are allowed to dry; this can be avoided by covering raw areas with vaselin with or without bandage.

The continuous use of suction and pressure was attempted on several occasions. Unfortunately, however, the type of cuff used in these studies cannot be tolerated for more than a few hours and immobilization of the extremity becomes extremely irksome after 2 or 3 hours. Until a more comfortable cuff is available, suction

and pressure therapy should not be used routinely for more than a few hours without interruption.

The effects of suction and pressure on intermittent claudication were difficult to evaluate and have been in general less striking, though slow improvement was observed as a rule. The subjective nature of the symptoms in intermittent claudication and the possibility of spontaneous recovery make it advisable to reserve judgment concerning the usefulness of suction and pressure therapy in treating this particular form of pain.

The effect of suction and pressure on actual lesions arising from prolonged ischemia depend upon the type of lesion. Patients with frank gangrene did not improve significantly during or after exposure to pressure variations. One patient with a large sloughing ulcer under the malleolus showed temporary improvement, but slow extension of the slough and renewed pain after several weeks made amputation eventually necessary. Those patients who had indolent ulcers without frank gangrene and without large sloughs were markedly improved. The ulcers under observation had, in some instances, been indolent or enlarging under treatment with antiseptics and heat for periods of several months before pressure variations were used.

Protocols. CASE 3.—(Table 1.) M. T., male, aged 60, with mild diabetes of unknown duration, developed a necrotic ulcer on the lateral aspect of the right heel while convalescing from the amputation of his left leg for gangrene at another hospital. The necrosis extended deeply; the lesion had not changed during 3 months' conservative treatment.

On admission to the Philadelphia General Hospital, physical examination showed retinal and peripheral arteriosclerosis with popliteal pulsation but no palpable pulse in the foot. Roentgenography revealed conspicuous calcification of the pedal arteries. The foot was not painful and was cyanotic only when dependent. No vasodilator response was obtained when vasoconstrictor tone was abolished, indicating that marked organic arterial occlusion was present. The punched-out ulcer was not tender and measured 1.5 cm. in diameter (Fig. 2*A*).

After 40 hours of treatment with alternate suction and pressure (−120 and +80 mm.Hg) during 6 weeks, the ulcer had healed completely (Fig. 2*B*) without modification of skin color. Anesthetization of the posterior tibial nerve still produced no elevation of skin temperature.

In this instance an ulcer unimproved by 3 months of usual treatment healed during suction and pressure therapy.

CASE 17.—(Table 3.) C. D., white male, aged 53, was admitted to the University Hospital on January 25, 1934. Since 1926, when the diagnosis of thromboangiitis obliterans was first made, the patient had undergone a series of amputations of fingers and toes. Certain of these amputations followed lumbar sympathectomy.

In December, 1933, the index finger of the right hand became painful and an ulcer formed at its tip. The finger was amputated, December 16, 1933, at another hospital. Operation was followed by infection of the palm, swelling of the whole hand and increased pain, particularly after the palm was incised for drainage.

On admission the patient complained of agonizing pain in the right hand. A large gangrenous slough extended from the base of the thumb to the base of the third finger. The distal cut end of the proximal phalanx of the second finger protruded from the middle of a slough which penetrated deeply into the middle of the palm. The other fingers of the right hand were cyanotic and showed pits indicating previous localized necrosis. Arterial pulsation palpable in the elbow could not be followed to the wrist. A roentgenogram showed osteomyelitis of two metacarpals.

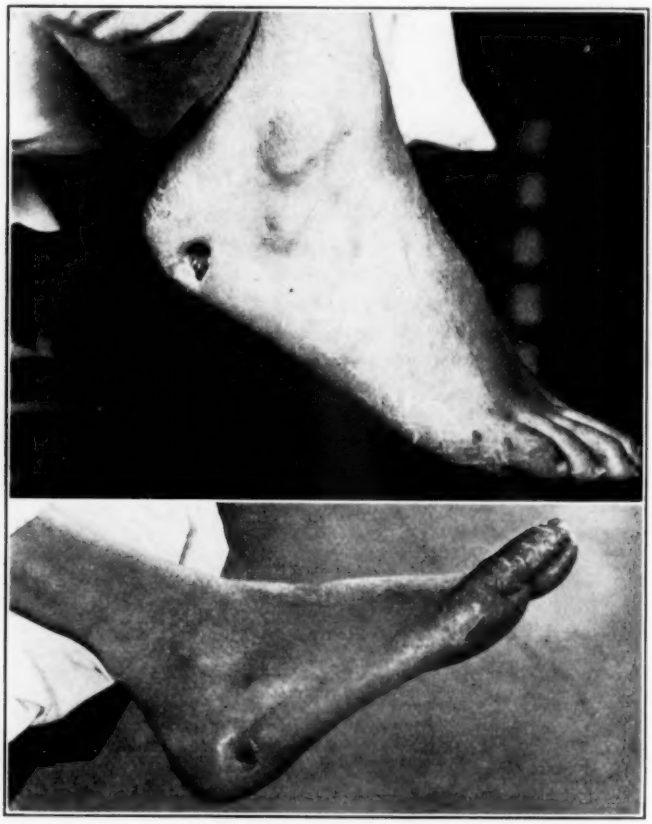

FIG. 2.—Patient M. T., Table 1, No. 3, showing lesion: (*A*) After ordinary conservative treatment for 3 months; and (*B*) after suction and pressure therapy, totaling 40 hours in 2 months.

Conservative treatment was regarded as completely hopeless, owing to the size of the slough and the well-developed osteomyelitis. There was no evidence of acute spreading infection though the whole hand was swollen and brawny as a result of previous infection. The patient absolutely refused to submit to amputation until 72 hours after admission. During this interval the right hand was exposed to suction and pressure to relieve rest pain if possible. When the patient lay in bed the hand could not be

held above the level of the sternum more than a few minutes without producing agonizing pain. On 2 occasions the right hand was placed in a modified aluminum box elevated above the sternum so that the hand assumed the position which, under ordinary conditions, became intolerable after a few minutes. Suction and pressure were applied while the hand lay in this position.

FIG. 3.—Patient C. L., Table 1, No. 4, showing lesions: (*A*) After ordinary conservative treatment for 3 weeks; and (*B*) after suction and pressure therapy, totaling 37 hours in 1½ months.

OBSERVATION 1, JANUARY 26, 1934.

12.15 P.M. Right hand placed in apparatus with sponge rubber cuff at a point halfway between the elbow and wrist. Suction (80 mm.Hg) and pressure (60 mm.Hg) applied alternately for 25 and 5 seconds, respectively.
12.30 P.M. No pain whatever.
1.45 P.M. No pain. Pump stopped for 2 minutes, followed by severe pain in palm.
1.47 P.M. Pump started again. Fingers still cyanotic with small red areas visible over palm.
1.48 P.M. Pain less.
1.49 P.M. Pain gone, itching remains.
2.30 P.M. Slight persistent pain in palm, not severe.
2.35 P.M. Hand removed. No severe pain at time of removal but pain returned later.

OBSERVATION 2, JANUARY 26, 1934.

9.00 P.M. Pain present. Suction (90 mm.Hg) and pressure (70 mm.Hg) applied alternately for 25 and 5 seconds, respectively.
9.05 P.M. No pain.
9.35 P.M. Itching in palm, no pain.
10.00 P.M. Slight steady pain on back of hand and palm obviously not severe since patient slept most of the time.
10.03 P.M. Pump stopped, aluminum chamber opened to loosen bandage over wrist.
10.04 P.M. Severe pain.
10.05 P.M. Pump started, pain diminishing.
11.15 P.M. Entirely comfortable, sleeping at intervals.
11.40 P.M. Hand feels numb and tired, especially near wrist where cuff is situated.
12 MIDNIGHT. Discomfort and numbness due to pressure of cuff required removal of hand from the apparatus. Numbness and fatigue disappeared as soon as cuff was removed from the forearm.

Suction and pressure relieved rest pain temporarily on 3 occasions, but pain in the intervals, the magnitude of the slough and the osteomyelitis made amputation obligatory.

CASE 29.—(Table 5.) G. M., white male, aged 65, observed blueness of the left great toe in October, 1932, with numbness and pain in the ankle after exercise. During April, 1933, he experienced sharp, lancinating pain in the left great toe which continued with exacerbations so that continued sleep was impossible, even with opiates, for the 2 weeks immediately preceding admission.

On admission to the University Hospital on April 27, 1933, physical examination revealed emphysema, enlargement of the heart to the left and a blood pressure of 176 systolic and 74 diastolic. There was moderate generalized arteriosclerosis and no arterial pulsation could be felt in either foot. A vasodilatation test revealed marked organic vascular occlusion. A diagnosis of arteriosclerotic occlusion was made.

The affected toe was extremely painful, tender on even light pressure and deep slaty-blue in color. Its appearance was that of an early stage of gangrene. During the first 48 hours of hospitalization the pain was not appreciably affected by considerable sedative medication and a thermoregulated warm cradle.

From April 29 to May 9 suction and pressure therapy was used from 2 to 4 hours daily. No pain was experienced while the extremity was exposed to suction and pressure. The patient slept throughout the first few periods of treatment. Tenderness disappeared and cutaneous blebs originally present dried up without involving more than the superficial layers of the skin. Skin color changed only slightly at first, but later the area of cyanosis was rapidly invaded by rubor and eventually the whole toe was at times bright red in color, still becoming rather cyanotic, however, in the dependent position. By May 1, rest pain, formerly severe and continuous, was much milder and only occasional. There was almost no pain after May 7 sedatives being discontinued after May 6. The patient was discharged, May 27, 1933, after being free of pain for 2 weeks. The color of the left foot was practically normal at the time of discharge.

Discussion. The desirability of increasing local blood flow in certain medical and surgical conditions involving the extremities has long been recognized. Paré,[9] Nicoladoni,[10] Bier[11] and others induced venous congestion by applying a constricting bandage at the

base of the extremity. While this procedure increases the amount of blood trapped in the vessels distal to the bandage it does not increase, but really reduces, total blood flow if congestion is extreme (Stewart[12]). Junod[13] and Bier[11] placed the limb in a rigid box and produced venous engorgement by removing air slowly over a period of 2 to 3 minutes until the pressure about the limb was finally reduced considerably below atmospheric pressure. Hemorrhages appeared in the skin when the pressure was reduced too greatly during such prolonged suction, indicating that the peripheral vessels were conspicuously distended. Bier claimed no increase of blood flow for this procedure, properly regarding it merely as another method of producing passive congestion.

Direct measurements of capillary pressure (Landis[14]) indicated that the rate of blood flow in the capillaries of the frog's mesentery depends upon the steepness of the gradient of peripheral blood pressure. According to Poiseuille's law the amount of fluid flowing through a rigid tube depends upon the fall in pressure along the tube. On these grounds Landis and Gibbon[3] were the first to call attention to the theoretical possibility of increasing the peripheral fall in blood pressure by applying negative and positive pressure alternately to the surface of the lower extremity. It seemed likely that this procedure, if carried out under the proper conditions, might increase the amount of blood flowing past an arterial obstruction in unit time. In normal subjects these pressure variations increased blood flow and elevated skin temperature in the treated limb. The same procedure diminished the rate of cooling of an extremity originally warm, and usually caused an originally cold extremity to become warmer. Pressure variations sometimes failed to affect the skin temperature of the cold extremity, but as soon as vasoconstrictor tone was diminished slightly, skin temperature rose conspicuously in the treated extremity. The vasodilator response to warming one forearm appeared earlier, and was more complete, in the extremity exposed to external pressure changes. The studies were then extended to include patients with peripheral vascular disease advanced to the stage when a rise of skin temperature could no longer be induced by abolishing vasoconstrictor tone. In these patients, alternate suction and pressure increased blood flow even though pronounced organic obstruction was present (Landis and Gibbon[4]). It was suggested that this procedure might help to alleviate the manifestations of the ischemia ordinarily observed in patients suffering with obliterative structural disease of the arteries.

Reid and Herrmann[15] simultaneously studied the effects of treating patients by applying intermittent negative pressure alone to the extremity, according to Bier's method. In their first report (1933) they advocated the following procedure: "The air is slowly withdrawn from the chamber so that about 2 minutes are required

to reduce the pressure within the chamber to 70 mm.Hg of negative pressure. . . . . The negative pressure of 70 mm. is allowed to act upon the vessels of the extremity for 1 minute and then the pressure is slowly *increased* until atmospheric pressure is reached. This phase of treatment should also be done in about 2 minutes. The entire cycle will then be completed in about 5 minutes. Five to 10 such cycles constitute 1 treatment." Reid and Herrmann advised against the use of intermittent positive pressure because "serious secondary arterial thromboses" were produced in 3 cases. In a 5-minute cycle the prolonged period (2 minutes) of positive pressure might well be injurious since the pallor of the skin, even after a few seconds of positive pressure, indicates that the skin becomes relatively, if not completely, ischemic.

Landis and Gibbon,[4] in using +80 mm.Hg for 5 seconds, observed no deleterious effects in normal subjects or in patients with peripheral vascular disease. Nor have any injurious effects been observed in the studies reported in this paper. Herrmann and Reid found also that a negative pressure of more than 100 mm.Hg was apt to produce hemorrhages into the skin. It seems likely that this was due also to the long period (2 minutes) of suction and to incomplete emptying of the veins during the period when atmospheric pressure prevails. Both in normal subjects and in patients (Landis and Gibbon[4]), suction amounting to −120 mm.Hg for periods of 25 seconds did not produce visible cutaneous hemorrhages. In the studies reported in this paper no hemorrhages were observed presumably because the peripheral vessels were well emptied between suction periods by applying positive pressure (60 to 80 mm.Hg) for 5 seconds.

In a more recent publication, Herrmann and Reid[16] describe a commercially available unit which they have arranged for the use of suction and pressure up to 100 mm.Hg. They recommend that the alternation of suction and pressure be made at the rate of 2 or more complete cycles per minute instead of 1 cycle in 5 minutes —their original interval. They recommend a negative pressure of 80 mm.Hg and a positive pressure of 20 to 40 mm.Hg, the latter being required to empty the veins completely, particularly in thromboangiitis obliterans. Elevating the limb aids the return of venous blood and is more feasible with a glass container such as they use than with the heavier aluminum box used in the observations reported by us. As in the original Bier technique, however, the pressure variations are introduced slowly, the whole cycle being required for the *gradual* change from −80 to +40 mm.Hg. The average negative pressure is, therefore, considerably less than 80 mm.Hg, which represents merely the peak of negative pressure reached. In the studies reported here, −120 mm.Hg indicates the negative pressure during the whole of the 25-second period. The change from positive to negative pressure is made rapidly (during 3 seconds) to avoid the loss of mechanical efficiency which must

accompany the slower changes in pressure. This procedure requires a larger pump, a more powerful motor and larger tubing between the pump and the treatment apparatus. There is no way at present of deciding which procedure will provide the best practical results. Rapid and greater changes of pressure modify skin color more strikingly than do slower changes. Other things being equal, the flow of blood should be increased to a greater degree by changing pressure suddenly since the average negative pressure is greater.

Most of the patients whose course during suction and pressure therapy is described in this paper had been treated conservatively by the usual methods without success. The apparent benefit derived is, therefore, more significant than it would have been if unselected cases had been treated. The rise in skin temperature (Landis[5]), the diminution of rest pain and the healing of previously indolent ulcers indicate that alternate suction and pressure increases the blood flow at least temporarily. At the present time it is impossible to do more than speculate upon the permanence of this improvement. Complete and lasting recovery depends upon the development of adequate collateral circulation.* Sufficient time has not elapsed to determine to what extent increased blood flow depends upon the continued use of pressure variations. In some patients, collateral circulation seems to develop slowly during and after treatment (Landis,[5] Table 4, Cases 22, 23, 24, 25). The majority of the patients who were studied with reference to their vasodilator response before and after brief periods of treatment showed no significant change. This means only that the increase in the rate of blood flow was not sufficient to be measured objectively by recording skin temperatures during vasodilatation. It is conceivable that temporary clinical improvement may occur without change in the vasodilator response which is, at best, a rather crude test for measuring small changes in blood flow.

* The importance of this factor is emphasized by the recurrences since observed in Cases 3, 12 and 18. These 3 patients showed no increase in vasodilator response during or after suction or pressure therapy and received no significant amount of therapy after they were discharged from the hospital.

In 1 instance (Case 3) a necrotic lesion of the great toe appeared 6 months later and advanced slowly in spite of suction and pressure therapy. Amputation of the leg above the knee revealed marked sclerosis of the femoral artery. In Case 12 gangrene of the toe appeared 4 months after the patient was discharged from the hospital. Ascending infection contraindicated suction and pressure and led finally to amputation above the knee. Case 18 suffered from the subacute form of thromboangiitis obliterans which had already required amputation of 3 digits in the course of 2 years. The patient returned 1 year after the second admission, described in Table 3, with a deep ulcer at the base of the fifth digit. Involvement of an interphalangeal joint and osteomyelitis of a phalanx contraindicated suction and pressure therapy. The fifth toe was amputated in January, 1935, local heat, vasodilator drugs and suction and pressure being used to aid healing of the wound.

In these 3 cases collateral circulation obviously did not develop to any significant degree and clinical improvement was only temporary. Whether or not continued treatment after the patients were discharged would have modified the final result is not known.

Contraindications. Contraindications to the use of suction and pressure can be given at this time on theoretical grounds only, since the number of cases treated is far too small to permit generalization. Pressure variations cannot be used indiscriminately or without careful medical supervision. There must be no active or spreading cellulitis in the limb. In 2 patients, both diabetics, a doubtfully indolent process was aggravated by the first few hours of treatment and amputation was probably hastened rather than delayed. Before suction and pressure is used it should be carefully ascertained that encapsulated pus is not present. Infective material might easily be massaged into the lymphatics more rapidly during pressure variations. Osteomyelitis, however slight, makes it unlikely that complete healing of cutaneous lesions can be obtained as long as drainage from beneath continues. When large masses of tissue are actually gangrenous, or sloughing, only temporary relief has so far been observed.

Indications. The procedure seems to be worthy of clinical trial, particularly for patients in whom treatment with ordinary conservative measures is ineffectual. Evidence is accumulating to show that if patients can be aided temporarily during episodes of pain or ulceration, time is gained for the natural development of adequate collateral blood flow and mutilating operations can often be avoided. In this connection alternate negative and positive pressure therapy can be of service even to those patients whose peripheral arteries have lost their power of dilatation owing to advanced obliterative arterial disease. Suction and pressure therapy should not displace but can be added to other conservative measures.

Summary. The extremities of 29 patients suffering from advanced peripheral vascular disease were exposed to alternate suction (−80 to −120 mm.Hg) and pressure (+40 to +80 mm.Hg) for 25 and 5 seconds, respectively. These pressure variations were used for periods of 1 to 2 hours, at first once or twice daily, then 3 times weekly and finally, as symptoms diminished, once weekly.

Cyanosis usually diminished; symptomatic improvement was sometimes observed, however, without significant change in skin color.

The rest pain of ischemia was usually abolished during actual use of suction and pressure and gradually became less severe in the intervals between exposure to pressure variations. Lasting relief of pain was not observed in the presence of deeply extending gangrene or large sloughs.

Ulcers, enlarging or indolent under ordinary conservative treatment, usually began to heal soon after suction and pressure therapy was instituted.

Intermittent claudication became, in general, milder and exercise tolerance was slightly, but definitely, increased.

Suction and pressure therapy was of no definite, lasting service

in patients with osteomyelitis, deeply extending gangrene or large sloughs.

This form of therapy must be applied with caution, small pressure changes being used at first. The presence of acute spreading infection or encapsulated pus must be definitely ruled out before pressure variations are used.

Suction and pressure therapy, if carefully applied, appears to be worthy of clinical trial in the treatment of peripheral vascular disease even when organic obstruction has advanced to the point where arterial blood flow can no longer be increased by vasodilatation. The method may be of service by increasing local blood flow temporarily during episodes of pain or ulceration so that time is gained for the development of adequate collateral blood flow.

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A TENTATIVE WORKING CLASSIFICATION TO FACILITATE THE TREATMENT OF PULMONARY TUBERCULOSIS.*

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In the following classification we have divided all patients into two races, white and negro, and each of them into two groups, the minimal and the advanced. The patients with advanced disease

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have been further subdivided on the basis of the type of the predominating disease into the proliferative and the exudative. Under each of these we have discussed the moderately advanced and the far-advanced stages. These in turn have been separated into those with and those without cavity formation and whether or not the disease extended below the third rib. Finally we have attempted to outline the treatment of the patients according as to whether or not the disease was retrogressing, stationary or advancing. The surgical procedures are arranged in the order in which we recommend them.

It has long been considered a doubtful procedure to suggest any form of surgical intervention for patients in the truly minimal stage of pulmonary tuberculosis. In this stage the slight infiltration does not extend below the level of the second chondrosternal junction if unilateral or below the level of the clavicles if bilateral. Cavitation is, of course, never present. The results of treatment in such patients at the Trudeau Sanatorium reveal that at the end of 15 years 92% are alive. It is doubtful if the results of treatment in any class of patients with pulmonary tuberculosis will be found to be much better than this. Accordingly it seems safe to watch such patients and refilm them from time to time. If the second film shows a definite increase of the disease, the plan of immediate treatment depends upon what the patient has been doing up to this time. If he has been active, he should be put at rest and carefully watched. If he he has been on strict rest, active surgical interference at once may be considered, particularly when time or finances are pressing or urgent. In such patients, especially those where there is some indication of pulmonary contraction (the trachea drawn toward the diseased side, the diaphragm elevated, the mediastinum shifted), a temporary phrenic operation may be all that is required to bring about recovery. Artificial pneumothorax may be also considered, as the favorable results following this operation in the early stages of the disease in negroes suggests that it may be safely applied to other races.

Patients in the advanced stage of pulmonary tuberculosis should be grouped, we believe, according to the type of the predominating disease, into the proliferative and exudative groups. This, at times, is not a simple matter and the doubtful cases may be placed in the exudative group and watched more carefully. In each of these two groups the division into moderately and far-advanced stages should be followed, for they are important in determining the form of treatment required. Again it is necessary for the same reason to separate those with, from those without cavitation. The presence of a cavity automatically places the patient in the advanced group and any cavity with a diameter over 4 cm. falls once more automatically into the far-advanced group. Patients in the proliferative, moderately advanced group without cavitation can usually be

safely treated somewhat longer without resort to surgical interference. If the disease improves, surgical treatment is not indicated nor is it necessary in patients in a stationary condition though they need more careful watching. If the disease advances in spite of other forms of treatment, surgical interference is required.

As a pulmonary cavity can practically never heal until its walls approximate, as a wet-walled cavity usually gives off more or less numerous tubercle bacilli which constitute a threat to the remainder of the lung as well as to the opposite side, it is at once apparent that such an approximation of the walls is highly desirable as soon as possible. As soon as the disease in any case of pulmonary tuberculosis extends below the third rib (which usually implies that it has passed beyond the extent of a single lobe) the disease becomes much more serious. This is taken into account in patients with cavitation. In all patients retrogression of the disease is a hopeful sign but too much must not be based upon it when it is not associated with a very definite decrease in the size of the cavity. Hence surgical treatment may be required for a persistent unchanging cavity. In stationary disease lasting over 2 or 3 months, if symptoms or tubercle bacilli increase, or in progressive disease, surgical treatment is indicated. When the disease extends below the third rib, active surgical treatment is demanded earlier and upon slighter symptoms. The patient in the far-advanced proliferative stage without cavity usually requires no surgical treatment except for displacement of viscera, when a phrenic operation may relieve the situation. We can picture a patient in whom a marked contraction, similar to that following an organizing atelectasis, may require an artificial pneumothorax. A patient with a proliferative far-advanced stage of the disease with cavitation may demand surgical treatment even when the disease is retrogressing.

All patients with the exudative type of disease should be considered to be in a more serious, a more rapidly changing, a more acute condition. In a certain number the condition improves very rapidly but in others it progresses just as rapidly. Hence it is highly important to watch these patients more closely than those with proliferative disease. Cavities frequently appear with startling rapidity and may enlarge very suddenly. On account of the rapid changes that often occur in patients between the ages of 12 and 19, especially in girls, it is well to place such patients under this head. For similar reasons all negro patients fall into this group. In this group artificial pneumothorax is the operation of choice. The phrenic operation is often of little aid. In certain acute unilateral cases when the patients are in good general condition, having been ill and confined to bed but a short time, when artificial pneumothorax cannot be produced and when the phrenic operation has been of no avail, thoracoplasty may be considered. In many of such patients the chances of recovery are very slim without some form

A TENTATIVE WORKING CLASSIFICATION TO FACILITATE THE TREATMENT OF PULMONARY TUBERCULOSIS.

THE WHITE RACE.

Patients in *Minimal Stage*.

A. Surgical treatment unnecessary (only 8% dead at end of 15 years). Watch and refilm.
B. Second film shows definite increase of disease:
Treatment depends upon what patient has been doing up to this time.
1. Active life at time of second film with increase indicates Rest (postural, etc.).
2. Rest treatment at time of second film with increase:
Active surgical interference to be considered.
1. Phrenic operation temporary.
2. Artificial pneumothorax.

Patients in *Advanced Stages*.

Type of predominating disease.

I. PROLIFERATIVE.

Patients in *Moderately-advanced* Stage.

Without Cavity

A. Retrogressing disease:
No surgical treatment; watch and refilm.

B. Stationary disease:
Watch carefully for 2 or 3 months; symptoms determine treatment. If persistent, temporary phrenic operation too soon rather than too late.

C. Progressing disease:
If this occurs in spite of Rest Treatment, active surgical treatment is suggested at once regardless of symptoms.
1. Phrenic operation—with more limited lesion.
2. Artificial pneumothorax.
3. Thoracoplasty questionable.

With Cavity (never over 4 cm. in diameter)

After the disease reaches a certain stage cavitation is the first step toward healing and automatically advances the case into the moderately or far-advanced group.

1. Disease not extending below third rib
A. Retrogressing disease:
No immediate surgical treatment. Watch. Refilm. Persistent cavity except possibly in good chronic suggest surgical treatment.
B. Stationary disease (unusual):
If symptoms slight or absent watch carefully for 2 or 3 months. If symptoms and or tubercle bacilli increase active surgical treatment suggested. (See under Progressing disease.)

Progressing disease:
Demands active surgical treatment.
1. Phrenic operation (with or without scaleniotomy) with smaller, earlier, thin-walled cavities.
2. Artificial pneumothorax.
3. Thoracoplasty.

2. Disease extending below the third rib or ribs:
More dangerous.
Active surgical treatment demanded earlier and on slighter indication.

Patients in *Far-advanced* Stage

(Bilateral, more than one lung in extent, fibroid.)

Without Cavity

Usually requires no surgical treatment except for displacement of viscera.

Phrenic operation?

With Cavity

Retrogressive, Stationary, or Progressive suggest surgical treatment, depending upon symptoms and tubercle bacilli.

1. Phrenic operation alone?
2. Artificial pneumothorax (always attempt before thoracoplasty).
3. Thoracoplasty (favorable type for).

II. EXUDATIVE.

More serious; usually more acute; usually associated with cavity. Type of disease usually determines type of cavity. All female teen-age patients to be treated as if exudative.

Patients in *Moderately-advanced* Stage

A. Retrogressing disease:
Highly dangerous on account of sudden changes.
Watch most carefully. Roentgen-ray by weeks. Symptoms very important.

B. Stationary disease:
Almost non-existent. Marked unchanging symptoms demand immediate, active surgical treatment.
1. Artificial pneumothorax (operation of choice).
2. Phrenic operation?
3. Thoracoplasty if unilateral (when artificial pneumothorax and phrenic fail).
4. Pneumectomy? (possibly also following unsuccessful thoracoplasty; theor.).

C. Progressive disease:
Active surgical treatment demanded at once.
1. Artificial pneumothorax (method of choice).
2. Phrenic operation?
3. Thoracoplasty (only if strictly unilateral on account of danger of contralateral spread.

Patients in *Far-advanced* Stage

A. Retrogressing disease:
1. Artificial pneumothorax.
2. Phrenic operation?

B. Stationary disease:
Non-existent.

C. Progressive disease:
1. Artificial pneumothorax.
2. Phrenic operation?

THE NEGRO RACE.

I. Patients in the *Minimal* Stage
A. Rest in bed one month.
B. Second film in one month shows increase:
Surgical treatment indicated:
1. Phrenic operation?
2. Artificial pneumothorax (operation of choice).

II. Patients in *Advanced* Stage
Treat as if all came under *Exudative* group (of whites).

of surgical intervention. As artificial pneumothorax has often so greatly increased the chances of recovery in such patients, it seems justifiable, if pneumothorax cannot be produced, to resort to thoracoplasty, in hopes that extension to the opposite lung may be prevented and that the collapse produced may act in a way similar to that brought about by artificial pneumothorax. A desperate condition demands taking considerable chances. Even when the disease in the exudative cases is retrogressing, and more particularly when it is apparently stationary, surgical measures must be thought of. While this holds for the moderately advanced stage, the only hope for the far-advanced group lies in artificial pneumothorax. Intrapleural pneumolysis must be considered in all cases of incomplete artificial pneumothorax.

This tentative working classification is not intended for the surgeon with experience in thoracic surgery nor for the specialist with long training, but rather for the physician either in the sanatorium or on the outside, who needs assistance in deciding about the treatment for some of his patients.

SUSCEPTIBILITY TO TUBERCULOSIS: RACE OR ENERGY LEVEL?*

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In dealing, as physicians, with the tuberculosis problem we have been so intent on the matter of early diagnosis and treatment of the individual patient that we have too often failed to see the larger aspects of the disease in its general relationship to man. Steady decline in its death rate has largely resulted from improvement in the hygienic care of the active cases to prevent spread of infection. There remain, however, important underlying factors affecting susceptibility and resistance to the infection which deserve careful study.

Man has not everywhere the same resistance to tuberculosis. We have long recognized this fact in contrasting the severity of the disease in the negro with its less deadly course in the white race. We also are aware of the loss of resistance that accompanies states of low vitality from whatever cause (worry, grief, poorly controlled diabetes, malnutrition, overwork, exhaustion, etc.) and of the curative value of building up the general physical state of the body.

* All mortality figures in this article were obtained from annual statistics as issued by the Federal Government. Conception figures were derived from statistics of live births by dating back 9 months and 10 days. For a description of the method of estimating storminess, or temperature variability, see Am. J. Hyg., **15**, 573, 1932.

There are, however, still other factors affecting the whole population which exert a marked influence on the general resistance to tuberculosis, factors that in the main affect the energy level of existence and the physical vigor of man. It is this aspect of the problem which will be taken up in the following paragraphs.

We have in various papers[1] shown how bodily energy depends on the stimulating character of the environment, with temperature level and variability as perhaps the most important factors. Metabolic diseases are found to vary in frequency and severity in direct proportion to the degree of this climatic stimulation, while for certain infectious diseases (acute nephritis and acute appendicitis) an inverse relationship was found. Where the climatic drive produces most severe metabolic disturbances, there do we find the general resistance to infections highest, while in the Gulf States, where diabetes and toxic goiter are of little importance, resistance to infection is low. With the wide and frequent storm changes of

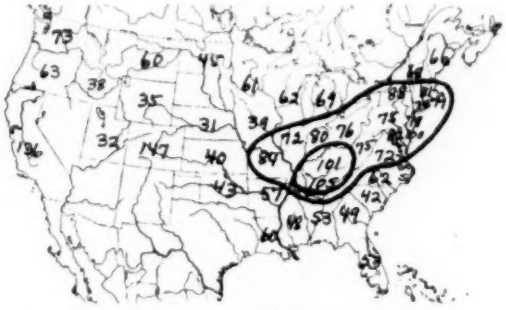


FIG. 1.—Death rate from tuberculosis (all forms) per 100,000 estimated population, by states. White race only—annual average, 1924–1928.

the Northern States, man must endure much more frequent infectious attacks, especially in the respiratory tract, but his high vitality counterbalances this frequency of attacks. Were the people of the Gulf States suddenly to be subjected to the weather fluctuations of a northern stormy season, the respiratory disease death rate would be terrific.

Let us now look into the climatic relationships of tuberculosis. There are first presented the state and city white death rates for the disease over a 5-year period (Figs. 1 and 2). The high rates for the Southwest (California, Colorado, Arizona and New Mexico) should be disregarded, as they probably represent migration to this area of tuberculosis individuals from other states. Otherwise, the highest state rates for the white population are found in Tennessee and Kentucky, with the secondary high zone covering most of the states to the north and east. Throughout the Western Plains the state rates are low, while along the Gulf they are only slightly higher.

Because state rates for tuberculosis are so often influenced by the distribution of the population between city and country, rates for large cities were calculated and are presented in Fig. 2. Here one sees a V-shaped arrangement of the high rates, with the apex at New Orleans and one arm covering the northeastern area that shows the high state rates. The other arm extends northwestward up the plains into the Canadian provinces. This is quite similar to the graphs of acute appendicitis attacks and deaths and to puerperal sepsis deaths. In general, this V represents the course of our cold polar waves as they sweep down out of Canada, pass down the Western Plains to, or near to, Texas, and then reverse their direction to pass back up the Mississippi and Ohio Valleys on their way to the mouth of the St. Lawrence.

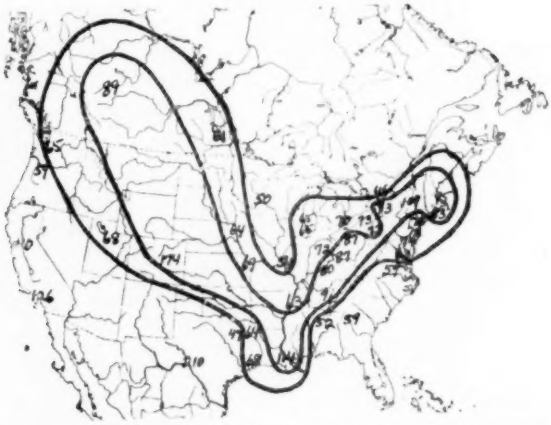


FIG. 2.—Death rate from tuberculosis (all forms) per 100,000 estimated population, in large cities. White race only—annual average, 1924–1928.

Negro rates, while everywhere roughly 3 to 5 times higher than the white, show a steady increase on passing northward from the Gulf. Note in Table 1 the steady increase from Georgia up to Maryland and from Alabama up to Kentucky. They also show a diminution westward from the Mississippi River. The Ohio Valley seems to be particularly bad for tuberculosis (see Table 1 for negro rates by states and cities). A study of reported case incidence and case fatality over the country is now being made, preliminary figures indicating a much lower case fatality rate in the northern stormy area than in the South.

In order to obtain a closer insight into the disease and its general characteristics, an analysis was made of the records of the Hamilton County Tuberculosis Sanatorium for the past 25 years. Cases were selected where a definite month for the onset of symptoms was ascertained and recorded, and the statistics were tabulated on the

basis of color, state of birth, duration of disease and time of onset. Fig. 3 shows the curve of frequency of onsets throughout the 12 months, based on 3179 cases. For comparison is given the graph of temperature variability, or storminess, for 8 northern cities (Boston, New York, Baltimore, Cincinnati, St. Louis, Minneapolis, Chicago and Cleveland) which would also hold fairly well for Cincinnati alone. Here is seen the close parallelism between storminess and tuberculosis onsets throughout the year, both reaching a peak in January and the low point of the year in July and August. The general curve of all respiratory infections, if plotted, would also follow much this same course, as would an inverted curve for the hours of sunshine.

TABLE 1.—DEATHS FROM TUBERCULOSIS (ALL FORMS) PER 100,000 ESTIMATED COLORED POPULATION. ANNUAL AVERAGE, 1924–1928.

States.

Maryland	269	Tennessee	295
Virginia	194	Alabama	165
North Carolina	169	Mississippi	156
South Carolina	144	Louisiana	177
Georgia	142	Arkansas	146
Florida	151	Oklahoma	146
Kentucky	270		

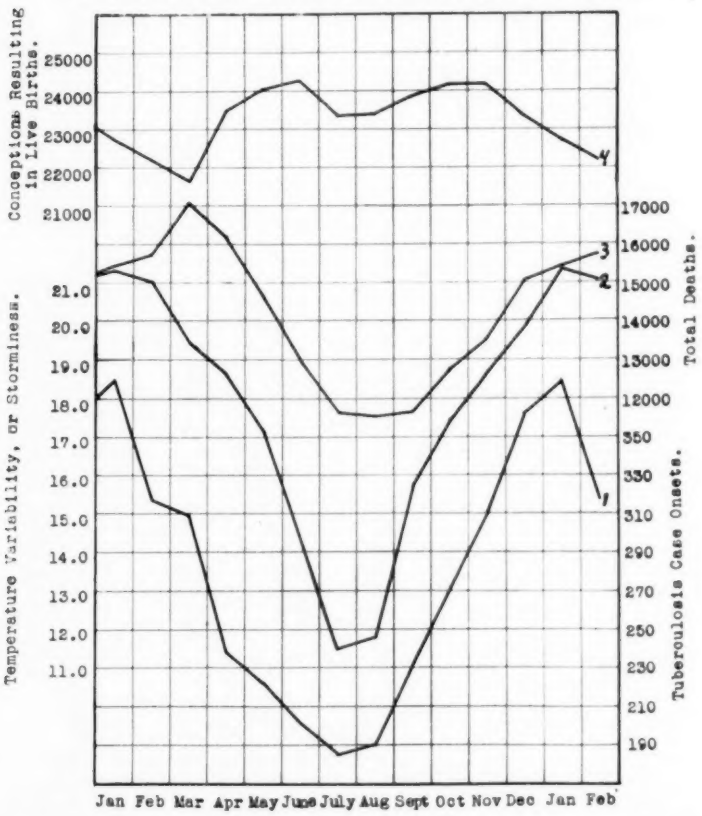
Cities.

Los Angeles	494	Washington	283
Cincinnati	456	Indianapolis	260
Cleveland	432	Memphis	244
Kansas City, Mo.	366	Birmingham	242
Chicago	355	Pittsburgh	231
Detroit	321	Atlanta	224
New Orleans	306	Dallas	221
Nashville	300	Richmond	215
St. Louis	299	Louisville	210
New York	299	Fort Worth	170
Philadelphia	297	Houston	124
Baltimore	291		

This seasonal difference in frequency of onsets, while it follows storminess very closely, does not coincide exactly with variations in general vitality in the population. In Fig. 3 are also shown the month by month rates for conceptions resulting in live births and for deaths for the 8 cities mentioned in the preceding paragraph. These two rates are functions of general vitality and are usually mirror images of one another, although in this instance the conceptions show a depression for the July and August heat as the mean monthly temperature rises above 70° F.[2] The general death rate and tuberculosis onsets are both lowest through mid-summer and rise steadily through the fall and early winter. The deaths continue to rise through March, however, while the decline in tuberculosis begins in February. The precipitous decline in case onsets comes in April, however, as the general death rate turns downward and the conception rate shows a sharp rise.

In view of the marked tendency for the disease to begin producing symptoms during the colder, more stormy months, it seemed advisable to see whether it was less deadly in summer than in winter. To this end cases were grouped according to month of onset and

FIG. 3.—SEASONAL VARIATIONS IN TUBERCULOSIS ONSETS IN RELATION TO CONCEPTIONS, TOTAL DEATHS AND TEMPERATURE VARIABILITY.

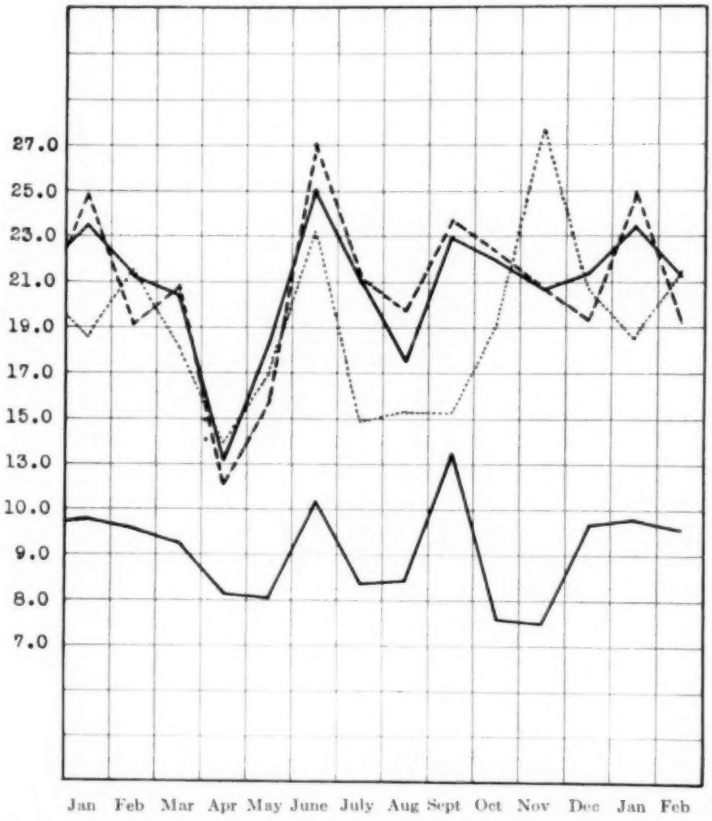


1, Tuberculosis onsets are for patients who died at the Hamilton County Tuberculosis Sanatorium from 1909 to 1934. 2, Temperature variability curve represents mean monthly values for the past 60 years for the 8 stations named in text. 3, Curve for total deaths represents 5-year average of total deaths, month by month, for same 8 cities from 1924 to 1928. 4, Conceptions resulting in live births also represent 5-year average.

months of duration between onset and death. In Fig. 4 are graphed the mean durations of the disease in months according to the time of year it started. All Ohio-born white cases from 1909 to 1933 are shown in the upper solid graph. In the dashed graph are shown the findings for the part of these white cases coming on from 1909

to 1920, inclusive, while the cases arising since 1920 are presented in the dotted graph. In the lower solid graph were included the findings from negro patients whose birthplace lay in Alabama, Georgia, South or North Carolina.

FIG. 4.—MEAN DURATION (IN MONTHS) OF TUBERCULOSIS IN CINCINNATI ACCORDING TO MONTH OF ONSET AND BIRTHPLACE.



Upper solid graph represents white patients born in Ohio who contracted the disease from 1909 to 1934. Dashed graph represents Ohio-born white cases with onset from 1909 to 1920, inclusive. Dotted graph represents Ohio-born white cases with onsets since 1920. Lower solid graph represents all negro cases with birthplace in Alabama, Georgia, South or North Carolina.

Certain striking features of these 4 graphs stand out clearly. First is the short duration of the disease in cases with onset in April. All groups, black and white, show this rapid course of the disease from an April beginning. Next is seen the uniform high peak in June for all groups, cases starting in June being in general of longer duration. July and August appear less favorable, while

in September the mean duration again shows a marked rise in all but one group. October and November are again characterized by shorter duration from onset to death, but through December and January the tendency seems to be for a slower course.

That these findings for two different time periods with Ohio-born white patients, and for the Southern-born negroes, should show such agreement throughout the year must indicate a definite trend in the disease course, depending on the month of onset. It must be significant, for instance, that the sharp lengthening in disease duration to its June peak should coincide with the year's highest conception rate. Likewise it is probably not by chance that cases of the disease beginning in July and August, when conceptions are depressed by the summer heat, should pursue a more rapidly fatal course. In the early fall, conceptions turn upward as the disease duration again lengthens. Then in late fall, the trends are reversed. Most striking of all, however, is the fall in resistance to tuberculosis that reaches its crisis in April. Persons contracting the disease in Ohio in April would seem to be subjected to distinctly greater hazards than those who become ill in June.

TABLE 2.—MEAN DURATION (IN MONTHS) OF TUBERCULOSIS ACCORDING TO BIRTHPLACE.*

Birthplace.	Color.	No. of cases.	Mean duration, mos.
Ohio	White	912	22.27 ± 0.66
Other Northern States and Canada	White	164	24.65 ± 1.50
Kentucky	White	217	21.34 ± 1.20
Tennessee	White	40	22.83 ± 2.65
Miss., La., Ark., Texas, Okla.	White	16	20.13 ± 4.62
Md., D. C., Va., W. Va.	White	36	15.00 ± 1.65
N.C., S.C., Ga., Fla., Ala.	White	19	11.82 ± 1.84
Central Europe and Great Britain	White	175	20.60 ± 1.21
Ireland	White	39	21.96 ± 2.74
Eastern Europe	White	51	19.44 ± 1.69
Mediterranean countries	White	50	11.74 ± 1.03
Ohio	Black	168	16.84 ± 1.64
Other Northern States	Black	41	11.50 ± 1.01
Kentucky	Black	298	11.21 ± 0.45
Tennessee	Black	88	10.10 ± 0.85
Miss., La., Ark., Texas, Okla.	Black	57	12.24 ± 1.61
Md., D. C., Va., W.Va.	Black	86	10.91 ± 0.72
North and South Carolina	Black	117	9.40 ± 0.48
Alabama	Black	177	9.09 ± 0.46
Georgia	Black	204	9.37 ± 0.41

* Taken from 2955 records of patients dying at the Hamilton County Tuberculosis Sanatorium.

It will be noted from Fig. 4 that the Southern-born negro patients exhibit always a shorter duration of the disease than do the Ohio whites. To investigate this point more thoroughly, cases were grouped on the basis of place of birth, color and duration of disease. The mean duration, in months, of the disease in the different groups is shown in Table 2. Here, again, certain facts stand out. The

disease in negroes everywhere shows a significantly shorter course than is seen in white patients from the same region. For both negro and white patients, who contract the disease and die in Cincinnati, there is a strong tendency for the duration to be shorter the farther south the birthplace of the patient. Thus for negroes, those born in Alabama succumb most rapidly, those from Georgia next, then the Carolinas, Tennessee, the Virginias and Maryland, Kentucky and, finally, those born in Ohio. The Ohio-born group lasts almost twice as long as do the native Alabamans. Data for white patients show much the same picture, although fewer cases were available. Ohio-born whites, however, last almost twice as long as do those from the Carolinas, Georgia, Florida and Alabama. The differences between white natives from Ohio, Kentucky and Tennessee are not of importance.

One group shown in the table deserves special mention. Migrants, both white and black, born in the South from Mississippi westward seem to show a much greater resistance to tuberculosis than do Southerners from the more eastern Gulf States. In them the duration of the disease is not far below that shown by natives of Ohio. This fits in with the fall in both colored and white state tuberculosis death rates from the Mississippi River westward (Fig. 1 and Table 1). Just what relation this greater resistance to the ravages of tuberculosis in the lower plains states bears to the storm stimulation they receive is a question demanding further study. The great bodily vigor in this region is quite as evident in animal life as in man, however, for here cattle and hogs thrive almost as well as in the North, quite in contrast to the other southern states.

Of still further interest is the way the data on European migrants bear out the findings of the American-born patients. The patients who were born in the British Isles and Central Europe showed a survival time close to that of the Ohio-born. With a birthplace farther eastward, in Russia, Poland, Roumania and Finland, the patients were slightly less resistant, fitting in with the lessened climatic vigor of their native land. But most striking is the duration of only 11.7 months for patients from the Mediterranean countries, a figure almost identical with that found for white migrants from our southeastern states. These differences between migrants from the British Isles and Central Europe and from the Mediterranean countries cannot but be of significance, since they coincide so closely with differences observed in American-born migrants. The conclusion would seem justified that ability to withstand the spread of tuberculosis infection is in some manner related to climatic vigor, quite independent of race or nationality. From other recent studies it would seem most likely that the basic factor at play is the energy level, which in turn is definitely dependent on the degree of climatic drive imposed on the population, especially throughout childhood and adolescence.

Just one further point must be included in this article. It bears on the conclusions given in the last preceding paragraph. When we speak of racial susceptibility to tuberculosis, we commonly think of the negro as having the least resistance to the disease. Mortality statistics, however, show that American residents of another race have over twice the tuberculosis death rate exhibited by the negroes. The Chinese in this country, as shown in Table 3, have the highest rate of all groups listed. Although tuberculosis in China is a serious disease, it does not there run such a rapidly fatal course as we see in the negroes of our northern states. China is a land of stable climate, with even fewer storms than our eastern Gulf States have, so perhaps it is to be expected that they pay a heavy price for migration into our stormy northern area. The mental remark of many readers to this mention of the Chinese will doubtless be that their habits of living account for their high rate; but they fit too well into the general disease picture for such a simple explanation to suffice.

TABLE 3.—DEATHS FROM TUBERCULOSIS (ALL FORMS) BY RACE, IN U. S. A. PER 100,000 ESTIMATED POPULATION.

	Negroes.	Indians.	Chinese.	Japanese.
1920	239.0	391.6	526.3	221.4
1929	185.7	331.8	358.6	152.0
Percentage reduction over 9-year period	22.3	15.3	31.9	31.3

One often hears the remark that the high tuberculosis death rate among the Indians is probably due to the relative newness of the disease with them, and that perhaps somewhat the same situation holds for the negroes. But here are the Chinese in this country with the highest rate of all, even though in their own country tuberculosis has long formed no mean problem. It would be well worth while to look further into the tuberculosis situation among Indians under different climatic conditions to see if they too show the same relationship to climatic stimulation as do the black and white races.

General Summary. Certain facts stand out from the data available on tuberculosis. Although the disease is more prevalent and causes more deaths in the cooler more stormy regions, still we find among such populations the highest resistance to its progress. The mean duration of the disease among Ohio-born whites was found to be 22.27 months, while Southern-born whites lasted only 11.82 months. Ohio-born negroes lasted 16.84 months, but Alabama-born negroes only 9.09 months. Likewise among European migrants, those from Central Europe lasted 20.6 months, but those from Mediterranean countries only 11.74 months. These differences in ability to withstand the progress of the disease are too great to be of chance occurrence. They also are significantly related to

the level of climatic stimulation, for the Mediterranean countries of Europe are quite similar to our Gulf States in this respect, and Central Europe only slightly below our northern storm belt. It is also of significance that people from the only part of the South which receives a fair number of storms—westward from the Mississippi River—should show a resistance to tuberculosis almost as great as that of Northerners.

It should be remembered that the data presented in this paper are based on case histories of patients that *died* of tuberculosis. Could it have been possible to include data as to the duration of the disease in patients yet living, the difference between the Northern and Southern born would most probably have been even greater. Anatomic evidence has also recently been set forth[3] to show a more chronic course of the disease in the Northerner, either white or black, with better tissue response to the infection. All factors considered, resistance to tuberculosis does seem to be closely related to metabolic level, this in turn being determined by the intensity of climatic stimulation.

In practically all tropical and subtropical regions where tuberculosis has been studied, the natives have been found to possess very little resistance to the disease. In adults it usually pursues a rapid course and is of the childhood type. Opie[4] emphasized this point for Jamaica negroes, contrasting a duration for the disease in them of about 9 months with one of 28 months among Philadelphia white patients. Colored troops from Africa, imported into Europe during the World War, showed an amazing lack of resistance to tuberculosis, for in them it became an acute infection. The longest duration of symptoms seen was only 3 months.[5] Numerous references[3] have been made to this extremely low resistance of tropical natives, and much speculation has taken place as to the reasons for it. In view of the findings reported on the previous pages, it would seem that the low metabolic and energy level of these people may well be the chief reason for their lack of resistance. Broadening the study to include other infectious diseases will probably clinch the point, for if people in regions of stagnant heat show a lessened ability to combat all other infections, then we must accept this as the basis for differences in tuberculosis.

In a very large number of the case histories investigated in this study, the onset of symptoms dated sharply from attacks of acute respiratory infection. This, together with the fact that the curve of onset frequency for tuberculosis is similar to that for other respiratory infections, would seem to link them closely together. In view of this it would seem advisable that particular care be exercised in tuberculosis hospitals and sanatoria to avoid all forms of respiratory infection. From our present-day knowledge, this would seem to mean the avoidance of our severe storm fluctuations in atmospheric conditions during the more changeable months, particularly those

of the spring. Likewise the more rapid course of the disease from an onset in the mid-summer heat indicates the advisability of protecting patients who already have the disease from the debilitating effects of summer heat waves. In other words, the indication seems plain that, for most efficient care of tuberculosis patients, hospitals and sanitoria should be conditioned for year-round control of their indoor atmosphere.

One more point should be stressed in this paper. Too great emphasis cannot be placed on the dangers encountered by people who migrate from regions of low climatic vigor into our northern storm belt where climatic stimulation is probably the most intense to be found anywhere on earth. In a recent paper[6] there was stressed the increased frequency of metabolic and nervous breakdown that accompanies such migration, as well as the greater severity and earlier death from arteriosclerosis among these people. The present findings in regard to tuberculosis only emphasize further the hazards of such migration. Tuberculosis among Southerners, both white and black, in their home states along the Gulf is not nearly such a problem as it is among those who have migrated northward. No doubt similar findings would be made for all other forms of respiratory disease if statistics were available.

The findings here presented for tuberculosis, added to those for the degenerative diseases, point out the public and personal health dangers of undirected migration. The time cannot be very far distant when the Federal Government will exercise a close supervision over population movements within, as well as into, the country for both health and economic reasons.

The statistics here presented seem to indicate clearly a marked difference in both whites and blacks in regard to resistance against tuberculous invasion. Energizing climates seem to instill into people an increased ability to fight the infection; but, if such climates are energizing because of wide storm fluctuations, the frequency of infection will be greater. Whether eventual stabilization will take place in stormy areas at a sufficiently high level of resistance to reduce the disease incidence remains to be seen. The constantly declining tuberculosis death rate should not be viewed too hopefully in this respect, since it may largely be due to improved care and personal hygiene of individuals rather than to mass changes in resistance.

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OBTAINING PERMISSIONS FOR AUTOPSIES.

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The medical profession of this country recognizes the fact that autopsies are of the greatest importance and that medical knowledge cannot progress in a satisfactory manner without them. But the obtaining of permission from the nearest relatives is often a difficult problem, especially in a small hospital which admits all sorts of cases, both private and charity, and including numerous accident victims. In such a hospital the request must usually be made by the resident staff since they are on duty for the 24 hours of the day, and since they may be the only physicians to come in contact with the family of the patient before death.

At the Millard Fillmore Hospital the interns are prepared for this duty, when they first enter the institution, by impressing upon them the importance of autopsies and explaining how valuable such examinations will be to them; in short, by selling them the idea. Then they are coached in the technique of asking for permission and of convincing the relatives of its importance and the necessity for it. They are required to make the request of the relatives of every patient who dies in the hospital and, following each interview, they must fill out the blanks in a report such as is shown in Table 1, and deliver it to the pathologist within 24 hours. It is natural for a man to perform a duty in a more conscientious manner when he must report it in writing and when it may affect his standing in the hospital and in the eyes of his superiors. This report serves as a check on the energy and effort of the intern; it explains to the pathologist why autopsies were not permitted in some cases; it shows how various factors affect the permissions or refusals of autopsies; and it gives the hospital knowledge of help or interference by its personnel or by outside persons.

When 310 of these consecutive reports had accumulated, they were analyzed for the purpose of getting information which might be of value in obtaining more autopsies. Only adult deaths were considered, for in this hospital the only children are newborn infants who present a very different problem. In this group of 310 deaths there were 180 refusals and 130 permissions, giving an autopsy percentage of 42. But, as shown in Table 2, in 30 of those where no autopsy was performed it was impossible to get in contact with the relatives and so no request could be made. If these 30 were removed from the series, there would be only 280 where a request was actually made and the percentage would then be 46 for the adult deaths.

TABLE 1.—INTERN'S REPORT ON INTERVIEW TO OBTAIN AUTOPSY.

Patient's Name_____ Age_____
Room No._____ Religion_____ Nationality_____ Case No._____
Service: *i. e.*—Med., Surg., or Obstetrical_____
Is this a Coroner's Case?_____ Attending M.D._____
Working Diagnosis:_____

Operation: If any_____
Immediate Cause of Death_____
Member of Family Interviewed_____
What Members of the Family were Present?_____

Was Autopsy Permission Granted?_____
To which particular argument do you attribute your success in obtaining the Autopsy?_____

What reasons did the Family give for denying the Autopsy?_____

Was this a patient on your regular service?_____
Did any outside person interfere?_____ Who?_____
Did any outside person help get the Autopsy?_____ Who?_____
Did you get help or interference from the Staff Doctor who attended the Patient?_____

Date_____ Intern_____

NOTE.—A complete report must be made to the Pathologist on each death within 24 hours after the interview.

The reasons for refusal by the relatives in 150 cases are shown in Table 2, and include the several reasons sometimes given by one family. Altogether 94 (63%) refused for sentimental reasons, or a general dislike of the idea. But in 26 someone else interfered when the nearest relative seemed willing to have the examination, and in 9 more the relatives feared the displeasure of absent members of the family. In 21 the family felt satisfied that they knew the cause of death and the disease conditions present. This should warn the attending physician against explaining the disease to the family in too great detail and with too great certainty. He must know how uncertain clinical symptoms sometimes prove to be and what unexpected lesions often appear at the autopsy. In 8 the patients themselves had expressed their disapproval of autopsies. In 4 the request was refused by relatives who had seen or heard about autopsies when they worked in hospitals and undertakers' establishments. In 2 more the family were dissatisfied with former autopsies where the incision was much more extensive than promised to them. This emphasizes the fact that autopsies should always be performed in as dignified and unobjectionable a manner as possible so that the entire personnel of the hospital, including the physicians and nurses, do not develop a great distaste of them. It also points out that if promises are not kept, it will result in less autopsies in the future. The series of 310 deaths included 4 Jews only, and 2 of these used their religion

as a basis for their refusal. One man offered to allow an autopsy if the hospital would waive payment of the bill for his wife's care.

TABLE 2.—REASONS FOR FAILING TO OBTAIN AUTOPSIES IN 180 CASES.

				Per cent.
A. Relatives not interviewed			30	16.6
		Per cent.		
Could not be located	12	40.0		
Too ill or shocked	8	26.6		
Escaped interview	7	23.3		
Prevented by physician	3	10.0		
B. Reasons for refusal in 150 requests for autopsies.				
No reason given			47	30.1
Interference from others			26	17.3
		Per cent.		
Family	16	10.6		
Staff man	5	3.3		
Undertaker	2	1.3		
Lawyer	1	0.6		
Priest	1	0.6		
Feared displeasure of rest of family			31	20.6
Patient had disapproved of autopsies			8	5.3
Did not care what caused death			7	4.6
Patient had suffered enough			5	3.3
Knew too much about autopsies			4	2.6
		Per cent.		
Worked in hospitals	2	1.3		
Worked for undertakers	2	1.3		
Would do patient no good			4	2.6
Former autopsies unsatisfactory			3	2.0
		Per cent.		
Mutilation of body	2	1.3		
No help in insurance	1	0.6		
Jewish religion			2	1.3
Wished cancellation of hospital bill			1	0.6

On looking over these refusals, it becomes apparent that the only way to overcome this attitude of sentimental objection seems to be the education of the laity and this can be accomplished only by constant, sustained effort on the part of the medical profession and their associates. Also the young physicians can be trained in the best manner of making the requests and in arguments which may overcome the sentimental distaste. As the number of autopsies increase, they will be accepted more and more as the proper and expected thing to do.

The reasons for allowing autopsies to be done in 130 cases are shown in Table 3. On studying these, it is apparent that in the great majority of them (101 or 78%) the relatives consented because they felt that the examination would be of benefit to them. They really wanted to know just what familial diseases might be there to menace them and they wanted to collect insurance or compensation, or they thought that the case might come into court where an autopsy is often necessary. Therefore it seems best to prepare all arguments with this in mind and to present the question to the family as if it were a great benefit to them, as indeed it is, something

for which they do not have to pay, an expensive examination which may be theirs for saying the word. It should be offered as a privilege to them, not as a favor to the hospital or the physicians. Each request should be prefaced by "Wouldn't you like to know?" and ended by a promise to give the family the findings in either a personal interview or by a letter written in simple non-medical words. It should be pointed out that the examination cannot possibly harm or bother the patient but yet can be of much benefit to the survivors. Also a sympathetic attitude should be maintained during the interview and unpleasant words avoided. The expression "operate after death" usually gives no offense.

TABLE 3.—REASONS FOR 130 PERMISSIONS FOR AUTOPSIES.

	Number.	Per cent.
To obtain accurate knowledge of cause of death	60	46.1
Wish to give help in treating others	39	30.0
To obtain help in collecting insurance	21	16.1
To determine what diseases were in the family	18	13.8
Granted without any particular argument	14	10.7
To please the attending physician	4	3.1
Because of being an unusual case	4	3.1
Because patient approved of autopsies	2	1.5
To avoid calling the coroner	2	1.5

Thirty-nine, however, permitted the examination in the hope that it might be of benefit in improving the treatment for others. So the unselfish argument may work when recital of the benefits to be attained, does not impresss the family. Fourteen assented without any particular argument. They seemed to consider that an autopsy should be done as a matter of course, as a natural sequence of death. Such an attitude is the result of education and of consideration of the subject during the years before the emergency of death overtook a member of the family. In 2 cases the patients themselves had expressed a wish to have an autopsy performed. Four consented to please the physicians who seemed to want one. The influence of the attending physician is great and no large number of autopsies can ever be obtained without his coöperation and help. The resident staff should have, at all times, the backing of the attending staff in the form of influence and added arguments. In many instances a few words from the physician even over the telephone, is sufficient to obtain permission. In this series of 130, the attending physician helped, materially, in 53. In 11 more, the autopsy was obtained by other persons persuading the nearest relative to consent. Seven of these were friends and 4 were members of the family by either blood or marriage. The coroner used a favorable influence twice and the undertaker, the special nurse, and a priest each once. In 4 cases, consent was given because an unusual case was recognized and in 2 cases an autopsy was permitted rather than have the coroner called.

In this series of 310 reports of interviews, other factors which might have a bearing upon either consent or refusal were studied in

detail. Sex made very little difference since there were only a very slightly higher percentage of permissions in males. The interns seemed to get just as many permissions on substitute services as on their own. The 130 permissions were divided equally between the ward and private patients, but two-thirds of the refusals were among the private patients and but one-third were in ward cases. So the private patient, with his supposedly greater intelligence and experience, is no more amenable to arguments and reasoning along this line than is the charity patient.

A slightly larger percentage of permissions were obtained in coroner's cases than in others. This can be explained by the possibility of legal action of some kind in a large number of accidental deaths. Slightly fewer permissions were obtained in cases which had been operated upon, probably because the operation usually had revealed the disease conditions present, and the family may feel that the physician had his chance at the operation and there is no need to examine the vital organs again.

There seemed to be very little difference in the percentages of permissions among the different services, with the exception of obstetrics. Here the husband seemed to realize that death had been caused by some sort of an accident and he gave permission in the hope that help might be given to some other woman to whom a similar accident might happen in the future. The nationality made comparatively little difference with the exception of the Jews and the Poles. No autopsies were obtained in the 4 deaths of Jews and the great majority of the Polish patients refused to allow them. The Americans showed slightly more permissions than refusals.

One would naturally think that better results could be obtained by interviewing the nearest relative alone, but such was not the case. Slightly better results were obtained when several members of the family were present, for, although there was some interference, in other cases help was given. Wives permitted a higher percentage of autopsies upon the bodies of their husbands than did husbands upon their wives. This may be explained by the fact that many wives consented in the hope of collecting insurance or compensation while the average husband could expect no monetary benefit. Also the average male is more predatory and would object to the supposed desecration of a body which had been under his care and protection. This is borne out by sons giving more refusals than permissions. Sisters usually refused as did sons-in-law, but the latter felt that they did not have the real right of decision and they feared criticism from friends and other distant members of the family. Daughters, fathers and brothers showed slight differences but mothers gave a few more refusals than permissions.

More refusals were encountered among the Catholics than the Protestants. This may be accounted for by the large number of comparatively ignorant foreign people among the Catholics of this city. Among the 122 Catholics interviewed, two-thirds refused

and only one-third gave permission. Among the 172 Protestants, slightly more than half (53%) refused while 47% consented. A comparison of the age groups showed little of interest until the ages of 70 to 80 when there was 3% of refusals as compared to 14% of permissions indicating that there is less objection to having autopsies performed in older people.

Summary. 1. The majority of relatives object to autopsies for sentimental reasons.

2. The majority of relatives who permit autopsies do so because they feel that they, as a family, will benefit from them.

3. All requests should be made of the relatives from the point of view that the family will derive the greatest amount of benefit from the autopsy.

4. Autopsies can only be obtained by constant effort on the part of the medical profession. Physicians must first be convinced of the importance of the examination and then they must use every effort to persuade the relatives to consent to them.

5. The resident staff can be trained in the technique of obtaining autopsies but they must always be able to depend on the attending staff for help and encouragement.

6. Requiring an intern to write a report of every interview will have a good effect upon him and will bring out many interesting facts concerning the obtaining of autopsies.

7. Physicians should not explain the cause of death with too much certainty to the family, as it may prevent autopsies.

8. The pathologist should confine his examination to the limits promised to the family and he should make the examination as little objectionable as possible to the spectators.

THE EFFECT OF STANDARDIZED EXERCISE ON THE FOUR-LEAD ELECTROCARDIOGRAM.

ITS VALUE IN THE STUDY OF CORONARY DISEASE.*

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THE difficulty of evaluating the condition of the coronary circulation from clinical data alone has been one of the reasons that

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efforts have been directed to utilize the electrocardiogram as a supplement. Recent studies of the 4-lead electrocardiogram have shown the merit of this approach[1]; the present report deals with the possibility of using an exercise test as a further adjunct in such examinations.

It has been shown that changes in the electrocardiogram similar to those described in spontaneous attacks of angina pectoris[2–8] can be elicited in an attack induced by exercise.[5,7,8,9] These observers found, however, that the electrocardiographic changes were not always present when the anginal attack appeared, that they sometimes occurred when the anginal symptoms were absent, that no quantitative relationship existed between the electrocardiographic changes and the anginal attack, and that the electrocardiographic changes did not coincide in time with the anginal attack.

It seemed to us that perhaps a better correlation might be obtained if the exercise were standardized and if 4 leads instead of 3 were employed, particularly since recent work[1,10–14] has shown that Lead IV (or Lead V) enhances the value of the electrocardiogram in coronary disease.

After preliminary trials, we decided to use an exercise which the patient could perform while lying in bed. The exercise consisted of raising a 3-pound dumbbell in each hand by extending the arms fully at right angles to the trunk a total of 60 times in 3 minutes. A 4-lead control record was taken in each instance before the exercise, another set was taken immediately after the exercise and a third set about 7 minutes later. Lead V was found to be more suitable than Lead IV for this test and was used throughout. This exercise test was carried out in 20 patients from the Adult Cardiac Clinic having a history of angina pectoris on effort. The effect of the test on the 4-lead electrocardiogram and on the development of angina was correlated with the appearance of the electrocardiogram at rest.

The results are shown in Table 1. It was found that this exercise led to an angina attack in 13 of these patients. The other 7, while complaining of fatigue in the arms from the effort, did not develop any anginal symptoms. The anginal attacks which occurred were mild, resembling the onset of spontaneous attacks. This is no doubt due to the fact that the amount of effort is limited by the development of fatigue in the arms.

The effect of the exercise on the electrocardiogram of patients as far as the standard 3 leads are concerned is in accord with previous work. We found that there is no parallelism between the development of anginal pain and electrocardiographic changes, sometimes one or the other is absent, sometimes both are absent, sometimes both are present. The addition of the fourth lead was found to be of value in at least 2 patients where the changes following exercise were limited to this lead alone (Table 2). In many of the other

TABLE 1.—SYNOPSIS OF RESULTS.

Patient.	Appearance of control electrocardiogram.		Changes in electrocardiogram after exercise.	
	Leads I, II and III.	Lead IV (V).	Leads I, II, III.	Lead IV(V).
	Angina Did Not Develop After Exercise.			
1	Normal; left axis shift	Normal	None	None.
2	Normal; left axis shift, T_3-	Normal	None	None.
3	Abnormal; L.V.P., *Q-R-S* slurred, low "voltage"	Normal	None	None.
4	Abnormal; left axis shift, *Q-R-S* slurred, Q_3 present	Normal	None	*T* smaller; *S-T* +.
5	Normal; T_3-, left axis shift	Normal	$S\text{-}T_{1,2}-$, T_3 smaller	*T* smaller, *S-T* +.
6	Abnormal; L.V.P., *Q-R-S* slurred, *T* small and −, $S\text{-}T_1-$, $S\text{-}T_3+$	Abnormal; *Q-R-S* small	*T* more + or became +, $S\text{-}T_1$ more −, $S\text{-}T_3-$, $S\text{-}T_2$ isoelectric	*T* deeper.
7	Abnormal; *Q-R-S* slurred, *T* −, $S\text{-}T_1-$, $S\text{-}T_3+$	Abnormal; *Q-R-S* mainly up, *S-T* −	*Q-R-S*$_1$ smaller, *Q-R-S*$_3$ taller, $S\text{-}T_1$ more −, $S\text{-}T_3$ more +	*S-T* less −, *T* deeper.
	Angina Did Develop After Exercise.			
8	Normal	Normal	None	
9	Abnormal; Q_3 present, T_3-, *Q-R-S* slurred	Normal	$S\text{-}T_3-$	None.
10	Abnormal; L.V.P., T_1-, $S\text{-}T_1-$, $S\text{-}T_3+$, *Q-R-S* slurred	Abnormal; *Q-R-S* 1st phase up, *S-T* −	None	None.
11	Abnormal; *Q-R-S* slurred, L.V.P., low "voltage"	Normal	None	None.
12	Abnormal; L.V.P., *Q-R-S* slurred, T_3 inverted	Abnormal; *Q-R-S* up	None	None.
13	Abnormal; L.V.P., *Q-R-S* slurred	Abnormal; *Q-R-S* inverted	$S\text{-}T_3-$, T_3 smaller	None.
14	Abnormal; L.V.P., *Q-R-S* slurred, $S\text{-}T_{1,2}-$, $S\text{-}T_3+$	Abnormal; *Q-R-S* mainly up, *S-T* negative	$S\text{-}T_{1,2}$ more −, $S\text{-}T_3$ less +	*T* very deep.
15	Abnormal; L.V.P., *Q-R-S* slurred, low "voltage," $S\text{-}T_3+$	Abnormal; *Q-R-S* up and small, *T* small	$S\text{-}T_{1,2}-$	*T* deeper.
16	Abnormal; *Q-R-S* diphasic and slurred	Abnormal; *Q-R-S* small, *T* +	None	*T* less +.
17	Abnormal; *Q-R-S* slurred, left axis shift, T_3-	Normal	T_1 taller, T_3 deeper, $S\text{-}T_{1,2}-$	*T* deeper.
18	Abnormal; L.V.P., *Q-R-S* slurred, *T* small, $T_{2,3}-$, $S\text{-}T_1-$, $S\text{-}T_3+$	Normal	T_3+, T_1 more +, $S\text{-}T_1$ more −, $S\text{-}T_3$ more +	*T* deeper, *S-T* +.
19	Abnormal; L.V.P., *Q-R-S* slurred, $S\text{-}T_{1,2}-$, $S\text{-}T_3+$	Abnormal; *Q-R-S* up	T_3-, $S\text{-}T_3$ isoelectric, $S\text{-}T_{1,2}$ more −	*T* deeper.
20	Abnormal; *Q-R-S*$_1$ small and diphasic, $S\text{-}T_{2,3}-$, *Q-R-S* slurred	Normal	*T* smaller, *Q-R-S*$_1$ inverted, $S\text{-}T_{2,3}$ more inverted	*T* smaller, *S-T* +.

L.V.P. = Left Ventricular Preponderance; − = negative; + = positive.

records the magnitude of the change in the fourth lead was of great value in confirming the impression that the exercise had caused electrocardiographic alterations. Nevertheless it must be pointed out that even when the 4 leads were used, exercise on occasion had no demonstrable action on the electrocardiogram. The deductions obtained from 3 leads still hold when 4 leads are used but the number of negative responses is reduced (Tables 2 and 3).

TABLE 2.—SUMMARY SHOWING LEADS OF ELECTROCARDIOGRAMS IN WHICH CHANGES OCCURRED.

	Electrocardiogram changed after exercise in:				Electrocardiogram in control.			
					Abnormal in			Normal in all leads.
	All 4 leads.	Only Leads I, II, III.	Only Lead IV (V).	None.	All leads.	Only Leads I, II, III.	Only Lead IV (V).	
Patients developed angina after exercise	6	2	1	4	7	5	0	1
Patients not having angina after exercise	3	0	1	3	2	2	0	3
All patients tested .	9	2	2	7	9	7	0	4

The changes in the ordinary 3 leads following exercise (Table 1 and Fig. 1) were: (1) An axis shift to the right in a few instances; (2) a change in the *T* wave in a direction opposite to the major *Q–R–S* deflections; and (3) most striking, a tendency of the *S–T* segment to shift in a downward direction, viz., a positive *S–T* segment became less positive, isoelectric or even negative, an isoelectric *S–T* segment became negative and a negative *S–T* segment became more negative. However, in 1 or 2 instances the *S–T* segment in Lead III shifted in the opposite direction when the *Q–R–S* was down and deep in this lead.

The changes in Lead IV (or V) (Table 1 and Fig. 1) were characteristic when they occurred. They consisted of a shift in the *S–T* segment upward so that at times the *S–T* segment became positive. The *T* wave usually became deeper (or a positive *T* wave less positive); however, in a few instances the *T* wave became smaller. In all instances where a change occurred, the most significant alteration was a positive angular movement of the *S–T* segment, making the angle between the *S–T* segment and the descending limb of the *T* wave more acute. This is clearly to be seen in Fig. 1.

The majority of the patients had abnormal electrocardiograms of varying degrees (Tables 1 and 2). Only 4 had 4-lead electrocardiograms within normal limits. Lead IV was never found to

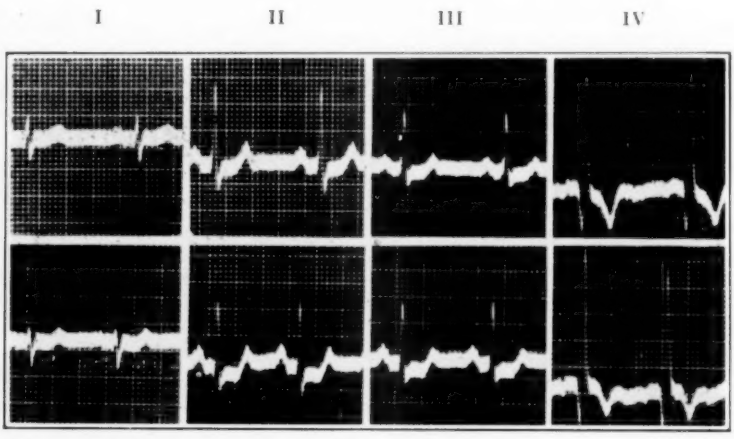

FIG. 1.—Segments of four-lead electrocardiogram, showing effect of exercise test on records in Patient 20. *A* is control before exercise; *B*, after 3-minute exercise.

TABLE 3.—SUMMARY CORRELATING (1) OCCURRENCE OF ANGINA AFTER EXERCISE, (2) APPEARANCE OF THE CONTROL ELECTROCARDIOGRAM AND (3) OCCURRENCE OF CHANGES IN THE ELECTROCARDIOGRAM AFTER EXERCISE.

	Patients developing angina after exercise.		Patients not having angina after exercise.		All patients tested.	
	4-lead electrocardiogram.		4-lead electrocardiogram.		4-lead electrocardiogram.	
	Normal.	Abnormal.	Normal.	Abnormal.	Normal.	Abnormal.
4-lead electrocardiogram shows changes after exercise	0	9	1	3	1	12
4-lead electrocardiogram does not show changes after exercise . . .	1	3	2	1	3	4

be abnormal when the other 3 leads were normal, but the reverse was true in many patients (Table 2). The appearance of the 4-lead electrocardiogram in patients with coronary disease is discussed in more detail in another communication where a larger series were studied.[1]

An analysis of the correlated data as assembled in Tables 2 and 3 leads to the following tentative conclusions:

The appearance of the 4-lead electrocardiogram taken at rest, the effect of a standardized exercise on the 4-lead electrocardiogram and the effect of such an exercise in producing anginal attacks are to be regarded as a triad which together augment the knowledge of the condition of the coronary circulation, obtained from clinical examination alone. The fact that a positive findings by one of these three criteria can occur with negative findings by the other two shows the value of relying on a combination of all three, rather than on any one of them alone. There can be no doubt that the fourth lead is a valuable addition to the other leads in carrying out this analysis. This deduction is to be considered no more than a preliminary approach, since the tests have been used in too few patients to warrant final deductions. This study has, however, pointed to the need of expanding the study to a larger group of patients.

One precaution is essential, as our preliminary tests showed, namely, to stop the exercise when generalized fatigue, dyspnea, cyanosis or anginal pain appeared before the 3 minutes were up.

Summary. The use of the effect of exercise on the 4-lead electrocardiogram was found to be a valuable adjunct in estimating the status of the coronary circulation. The routine use of some such simple exercise test may be found to be of value in judging a patient's response to effort.

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THE EFFECT OF SCARLET FEVER UPON THE HEART.*

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Although it is often stated that scarlet fever is a potential cause of heart disease, existing clinical descriptions of so-called "scarlatinal endocarditis" are far from agreement. It was in the hope of defining the condition more clearly that this study was undertaken.

The importance of the problem is attested by reports from various quarters of the incidence of endocarditis in scarlet fever.[1,2,3,4] Some of these are briefly summarized in the table. While such statistics are of considerable interest, the diagnosis of acute endocarditis in the presence of infection is fraught with such difficulty as to raise serious question as to their quantitative value. To meet such objections the disease has been studied from two points of view: first, from the electrocardiographic angle during the acute phase, an approach which has the advantage of complete objectivity; and second, from an estimation of the end results in the form of chronic valvular disease following upon scarlet fever.

1. Electrocardiographic and Clinical Study During Course of Disease. It was hoped that the electrocardiograph might afford some new evidence as to the type and perhaps the incidence of the cardiac involvement. The method had been employed by Shookhoff and Taran (1931) in 50 consecutive cases of scarlet fever.[5] They found no prolongation of the $P-R$ interval but did observe in Leads I and II minor changes in the position of the $R-T$ or $S-T$ interval in 14% and "abnormalities in shape and direction of the T-wave" in 10%. "All abnormalities occurred early in the course of the disease and disappeared early in convalescence."

A group of 171 scarlet fever patients has been studied electrocardiographically at the South Department of the Boston City Hospital. The cases were observed during the years 1932, 1933 and 1934, a time when scarlet fever was relatively mild in character. There was no selection of cases except in favor of arthritis, all cases

* This work was done under a grant from the David Bradford Osgood Fund.

of scarlatinal arthritis who came under observation during this period being included.

Abnormal electrocardiograms were found in 11 cases, an incidence of 6%. These abnormalities consisted of prolongation of the $P–R$ interval beyond 0.20 second in 5 cases and T-wave changes in 6 cases. The T-wave changes in Lead I or II, or both, consisted of marked temporary diminution in amplitude in 2 cases, flattening in 1 case and inversion in 3 cases. In addition, 8 cases exhibited a $P–R$ interval of exactly 0.20 second (a suggestive finding, at least, in the 5 cases who were less than 14 years of age).

Arthritis. Included in this group were 29 cases of scarlatinal arthritis. Of these only 2 showed definite electrocardiographic changes and 3 a $P–R$ interval of 0.20 second.

Age. The ages of all those who developed abnormal records were between 4 and 16 years. Seventy-five per cent of the patients fell within this age period.

Sex. Six of the cases showing abnormal electrocardiograms were males and 5 were females.

TABLE 1.

Author.	Source.	Number of cases of scarlet fever.	Number of cases of endocarditis.	Percentage of cases of endocarditis.	Number of cases of pericarditis.	Percentage of cases of pericarditis.
McCollum[1]	Boston City Hospital	3,000	16	0.50	18	0.60
Broadbent[2]	Metropolitan Asylums' Board	22,096	129	0.58	..	0.08
Broadbent[2]	London Fever Hospital	("period of 5 years")	....	1.80	..	0.15
Nobecourt[3]	French Army	278	7	2.50	2	0.70
Joe[4]	Edinburgh City Hospital	24,102	61*	0.25*	61*	0.25*

* Figures include both endocarditis and pericarditis.

Severity. There appeared to be no relationship between the severity of the scarlet fever and the incidence or degree of electrocardiographic abnormalities.

Time of Onset. Perhaps the most interesting feature of the study was that no abnormality was found in any electrocardiogram taken before the 13th day of the disease (although 61 records were taken during the first 12 days) (Fig. 1). The majority of the abnormal records were grouped between the 18th and the 34th days. This delayed reaction is comparable to that seen in the cardiac involvement of diphtheria or the recrudescence of rheumatic fever following a respiratory infection. It is in contrast to the immediate electrocardiographic changes sometimes noted in very severe acute infections, such as lobar pneumonia.

Fever. The delayed appearance of the electrocardiographic changes was associated with a recrudescence of fever in 5 cases. In 3 cases where the temperature curve was not complicated by secondary infection or possible serum reaction, the time from the onset of the scarlet fever to the onset of the secondary reaction was 16, 24 and 29 days, respectively. Figure 2 illustrates this reaction and its relation to the electrocardiographic changes. In this instance, the secondary reaction was not accompanied by arthritis, the only clue to its real significance being furnished by the electrocardiogram.

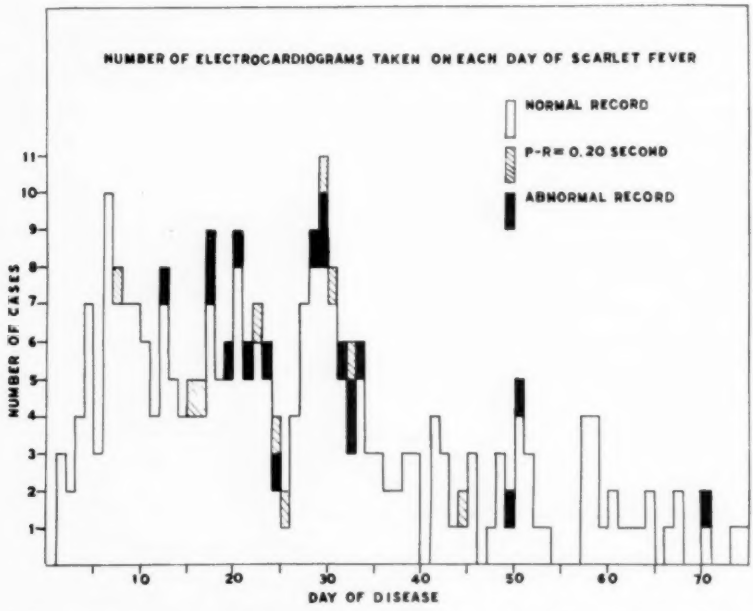
NUMBER OF ELECTROCARDIOGRAMS TAKEN ON EACH DAY OF SCARLET FEVER
NORMAL RECORD
P-R = 0.20 SECOND
ABNORMAL RECORD
NUMBER OF CASES
DAY OF DISEASE

FIG. 1.—Latent period between the subsidence of the acute scarlatinal infection and the appearance of a secondary reaction characterized by fever, tachycardia and prolongation of the *P–R* interval without, in this instance, any arthritis.

Particular emphasis has been laid on the electrocardiographic findings on account of their objectivity but the clinical evidence of cardiac involvement is nevertheless of some interest.

There were 6 cases of old rheumatic heart disease. Of these 5 showed no clinical or electrocardiographic signs of reactivation. The 6th case developed both clinical and electrocardiographic signs of reactivation with a complicating pericarditis.

There were 4 cases which developed clinical signs of endocarditis immediately following the scarlet fever. Of these cases 3 exhibited both systolic and diastolic murmurs at the apex, the 4th developed a very harsh systolic murmur at the apex. One of them showed

enlargement of the transverse diameter of the heart by Roentgen ray measurement (cardio-thoracic ratio 59%). Another showed a distinct "mitral bulge" in the upper left border of the Roentgen ray silhouette of the heart. Of the 4, 2 had electrocardiographic evidence of involvement and 2 had none.

Five cases who showed positive electrocardiograms had no clinical signs of cardiac involvement and 3 others showed only systolic murmurs.

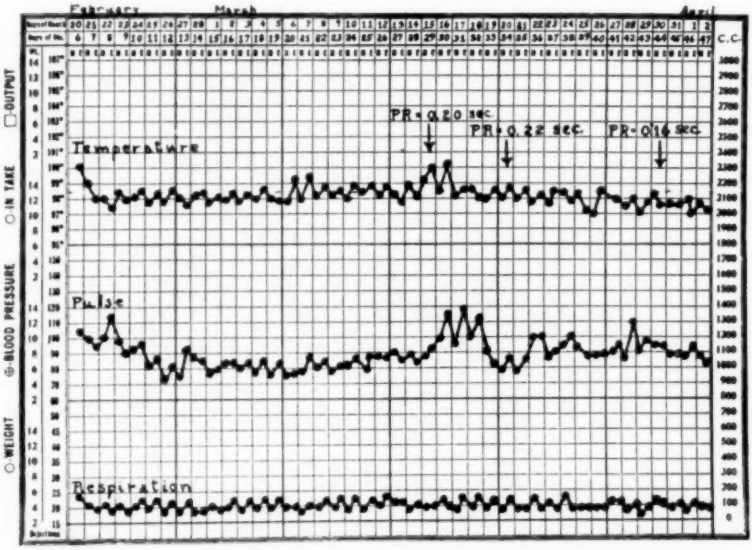

FIG. 2.—Delay in appearance of electrocardiographic abnormalities following scarlet fever. The tendency for these abnormalities to disappear is also suggested. Of 61 records taken between the 2d and 12th day of the disease, inclusive, none was abnormal. Of 138 records taken between the 13th and 33d days, inclusive, 15 were abnormal. Of 70 records taken between the 34th and 75th days, inclusive, only 3 were abnormal.

Seventeen patients, who showed no electrocardiographic abnormalities, developed systolic murmurs of differing grades of intensity, most of them apical, but without other signs of valvular disease.

2. FOLLOW-UP STUDY. Another approach to the problem of the rôle of scarlet fever in the production of heart disease is through a follow-up study of a large number of cases. This was done on a very small scale in Nobecourt's thorough investigation outlined in the table. He found that only 2 of the 7 soldiers who had "acute scarlatinal endocarditis" developed chronic endocarditis.

The present report is based on a follow-up examination of 600 cases from 1 to 3 years after scarlet fever. The examinations were carried out in the years 1931 and 1932 on individuals who had previously been treated at the South Department of the Boston

City Hospital for scarlet fever. These people returned to the hospital for examination in response to letters requesting them to do so. No selection of cases was made and the group appeared to be a representative cross-section of the patients who had passed through the scarlet fever wards during the period.

All persons in whom there was either a doubtful or positive diagnosis of cardiac disease were examined by at least two of the authors and received electrocardiograms and Roentgen ray measurements of the heart. The results of the follow-up study were compared with the original hospital record in each instance.

Of the 600 cases, only 7 had developed signs of chronic valvular disease during the interval. In 2 cases the signs of endocarditis had developed in the hospital before discharge from quarantine. In a third a typical attack of rheumatic fever had followed immediately after his discharge from the ward. Another had suffered from 3 attacks of rheumatic fever during the interval between the scarlet fever and the follow-up examination. In the remaining 3 cases, the physical signs of valvular disease were found without any intercedent history of rheumatic fever or chorea.

Of these individuals, 6 were girls and 1 a boy. Their ages were from 3 to 11 years, with an average of 5.6 years. Three of the cases had been classified as mild scarlet fever, 3 as moderately severe, and 1 as severe. With 1 exception (a case complicated by mastoiditis and operation) the patients were in the hospital the usual length of time (from 28 to 47 days). Except for the case of mastoiditis just mentioned there were no other important complications in the group who developed heart disease. There was no arthritis or nephritis in this group. Only 1 case exhibited a rise in temperature after the initial pyrexia had subsided and this was 1 of the 2 cases in which the diagnosis of acute endocarditis was made.

The type of heart lesion was indistinguishable clinically from "rheumatic" heart disease. Four of the patients had the characteristic auscultatory signs of mitral stenosis and regurgitation. Another had these signs and also those of aortic regurgitation; 1 had signs of aortic regurgitation alone and 1 of mitral regurgitation alone. It may be pointed out that the occurrence of heart disease in the group under consideration was far greater than would be expected in an unselected group of Boston school children of the same age and social status observed for a like period.[6]

All but one showed Roentgen ray evidence of heart disease. The only electrocardiographic abnormalities found on the follow-up examination were right axis deviation in 2 cases, the slurring of the Q–R–S complexes in all leads with a Q–S interval of 0.10 second in 1 case.

Hector[7] found that "The almost invariable result of scarlet fever upon the heart already damaged by rheumatism is a rekindling of the old trouble which in some cases had been quiescent for a

considerable period." This has not been our experience. In the follow-up series 4 instances were encountered in which rheumatic heart disease preceded the attack of scarlet fever. In 1 of these a recrudescence of rheumatic fever appeared immediately after discharge from the hospital. In none of this small group, however, did the follow-up examination indicate that the cardiac status had been significantly altered by the scarlet fever.

Discussion. All the findings in the acute and late phases of cardiac involvement in scarlet fever are analogous to the changes seen in rheumatic fever following acute tonsillitis. The importance of hemolytic streptococcus infections of the upper respiratory tract in precipitating rheumatic fever is well recognized. In both conditions there is often a well defined latent period of several weeks between the respiratory infection and the secondary constitutional reaction. In both, similar electrocardiographic signs of cardiac involvement may appear following a latent period. In both, endocarditis may occur with or without an acute migratory arthritis.

The arthritic manifestations in scarlatinal and rheumatic arthritis are so similar that in individual cases the differential diagnosis would be impossible without the history. However, if a large group of cases of scarlatinal arthritis is studied, certain differences from typical rheumatic fever stand out. These differences consist of a relatively greater incidence of involvement of the small joints in the case of scarlet fever, with a generally milder course and less effusion into the joints.[4] Also our figures, showing abnormal electrocardiograms in only 2 cases out of 29 of scarlatinal arthritis, are not as high as one would expect in rheumatic fever. On the other hand, there are plausible explanations for these discrepancies. The comparative youth of the scarlatinal patient would tend to mitigate the severity of the arthritis if it is of the type associated with rheumatic fever. (The average age of the 600 scarlet fever patients in the follow-up study was only 6.3 years.) It has been our experience, too, that electrocardiographic changes are less common in the younger patient with rheumatic fever. The striking similarity of the two conditions is obvious; the question of whether their differences are fundamental is doubtful.

Of the valvular involvement resulting from scarlatinal endocarditis one can only say that it is indistinguishable clinically from rheumatic endocarditis. The same may be said for the pericarditis associated with both conditions. The fact that scarlet fever caused a reactivation of infection in patients with rheumatic heart disease in only a minority of cases is only in keeping with the effects of other streptococcus infections of the respiratory tract in such cases. In hospitalized cases of rheumatic infection, streptococcus respiratory infections were followed by recrudescence of rheumatic manifestations in only 50%. One would expect the incidence to be less in cases of presumably inactive rheumatic heart disease.

Finally, it has been our privilege to observe in a recent case of post-scarlatinal endocarditis the appearance of typical rheumatic subcutaneous fibroid nodules.

The similarity and possibility of relationship between rheumatic and scarlatinal heart disease has been commented upon by others.[7,8,9,10] The evidence is now complete enough to indicate that they are probably identical. Interpreted in the light of Swift's allergic hypothesis, this means that a properly sensitized individual may respond to an infection with Streptococcus scarlatinæ by the allergic reaction known as rheumatic fever. There is no evidence that this reaction differs significantly from rheumatic fever following other streptococcus infections of the upper respiratory tract. Such a concept explains, in part, the absence of Aschoff bodies and other characteristic features of rheumatic fever in routine postmortem studies of scarlet fever.[11] The altered tissue reaction which characterizes rheumatic fever would only rarely be met with under such circumstances.

Summary. An electrocardiographic study was made of 171 cases of scarlet fever during and following the acute infection. Abnormal electrocardiograms were noted in 11 cases. The abnormalities consisted of prolongation of the P–R interval in 5 cases and flattening or inversion of the T wave in 6 cases and did not appear before the 13th day from the onset of the scarlet fever in a single instance.

A follow-up study of 600 cases of scarlet fever was made from 1 to 3 years after the acute infection. It was found that 7 of these individuals had developed heart disease in the interval. The type of heart disease found was indistinguishable clinically from rheumatic heart disease.

Since this paper was written a valuable contribution to the problem has been published by Paul and his coworkers which in general supports our conclusions. (Paul, J. R., Salinger, R., and Zuger, B. Relation of Rheumatic Fever to Postscarlatinal Arthritis and Postscarlatinal Heart Disease—Familial Study. J. Clin. Invest., **13**, 503, 1934.

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THE MIGRAINE PHYSIQUE.

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The riddle of migraine has developed a truly enormous literature[1] dealing with the many aspects of the problem. The functional nature of the attack,[2] the relation of the migraine seizure to epilepsy,[2] the etiologic significance of heredity,[3,4] allergy,[5–9] gonadal function, ocular defects[10,11] and fatigue,[12] and the prophylactic and active therapy[2] all have been repeatedly and voluminously discussed. However, it has not been possible to find any discussion of a characteristic physique in relation to migraine. Our own observations have strongly indicated that there is such a characteristic physique, or constitutional type, in which migraine appears with extraordinary frequency. It has been commonly possible to predict migraine in persons after but a cursory inspection and analysis of certain typical features.

Migraine long has been known to be familial and much has been written emphasizing the hereditary nature of the disturbance. Allergic tendencies are likewise recognized as being hereditarily transmissible, and the relationship of allergy to migraine seizures recently has received much emphasis. It is thus not surprising that along with these two significant observations there should be a characteristic constitutional type in which migraine, in one or more of its many forms, occurs with unusual frequency. Naturally, not all migrainous individuals conform to this characteristic type any more than all instances of cholecystitis appear in short, stout individuals, or pulmonary tuberculosis in those of the Stillar physique, but the incidence is amply high to justify correlation.

The stimulating work of Draper[13] and others[14,15] reminds us of the importance of fundamental constitutional characteristics in the causation of disease. Recognition of well-defined constitutional types does not aid appreciably in direct therapy, but should aid in creating a somewhat clearer understanding of the disease.

The frequency of the various characteristics of the migraine physique have been noted and tabulated in an unselected consecutive series of 100 cases of migraine seen in private practice. These data emphasize the frequency with which certain features are notable. The outstanding characteristics of the physique may be described briefly as follows:

1. Neither height nor weight are unusual, although extremes of variation are perhaps more frequent than in normal persons.

2. The hair is almost invariably characteristic—very fine and slender, straight and typically brunette. Migraine is most unusual in true blondes. The hair is neither unduly scant nor heavy, but is frequently rather more oily than usual. The significant feature is the soft, fine texture; it is never stiff and rarely naturally curly.

3. The eyes reveal unusually large pupils in proportion to the exposure to light. It has been noted repeatedly that this pupillary dilatation is exaggerated still further with fatigue and is especially marked just prior to an attack of migraine. Habitual pupillary dilatation occurred in 96% of the patients tabulated, and in the remaining 4% there was 1 instance of Argyll-Robertson pupils due to syphilis. These dilated pupils, however, react normally to light and accommodation, although they do not contract as firmly as the normal.

4. The skin is typically thin and fine and unusually smooth—more like a child's skin than that of an adult. It gives the impression of unusual transparency. Pallor is more common than ruddy facies. The facies are most commonly characterized by finely chiseled classical features with delicate moulding, narrow nostrils and small nasal alæ.

5. The extremities are habitually cold and frequently moist and clammy. Such cold and moist extremities were noted in 91% of these patients.

Other less obvious characteristics of these patients are an unusual lability of the arterial tension and pulse rate.[16] (See Table 1.) Of the instances of hypertension, 7 cases were of the emotional type, described previously.[17] The notable frequent coincidence of arterial hypotension is significant.[18] A history of attacks of typical paroxysmal tachycardia[2,19] was obtained in 49% of these patients.

The usual pallor of the skin may or may not be associated with the high incidence of secondary anemia. Apokamnosis and habitual fatigue are characteristic, occurring in 82% of the patients.[12] It is probable that there exists a distinct relation between the tendency to arterial hypotension and anemia and this marked diminution of endurance. The typical migraine patient fatigues readily and is, in fact, habitually tired. Almost all of the female patients (91% women) complained of marked exaggeration of this sense of fatigue or exhaustion just prior to their menstrual periods. Upper respiratory tract infections and chronic infections were conspicuously unusual, although rheumatic infection was surprisingly frequent. Some form of rheumatic carditis and chilling or chorea occurred in 15% of these patients, whereas all other infections totaled but 17%.

A tabulated summary of these 100 cases of migraine will illustrate the significant characteristic features.

TABLE 1.—CHARACTERISTIC FINDINGS IN 100 CASES OF MIGRAINE.

1. SEX.* Male, 14%; female, 86%.
2. AGE. Average, 31.4 years (extremes, 58 to 18).
3. CIRCULATORY OBSERVATIONS. Arterial tension: Average, 124.6/78.4 (extremes, 210/125 and 90/60); normal tension, 41% (increased 19%; decreased 38%). Pulse rate: Average, 85 (over 90, 21%; 70–80, 73%). History of paroxysmal tachycardia, 49%. Cold, moist extremities, 91%. Hemoglobin: Average, 72.3% (Dare); above 80%, 18%; 70–80%, 26%; 60–70%, 31%; undetermined, 25%.
4. NEUROLOGIC OBSERVATIONS. Pupils large, 96%; normal, 3%; Argyll-Robertson, 1%; History of scotomata, 54%. History of vertigo, 72%.
5. HAIR. Brunette, 93%; blonde, 7%; typically fine and straight, 96%.
6. MARKED APOKAMNOSIS, 82%.
7. POSITIVE FAMILIAL HISTORY, 89%.
8. WEIGHT. Normal, 38%; obese, 25%; underweight, 37%.
9. MENSES. Normal, 6%; marked intoxication, 91%; dysmenorrhea, 63%.
10. COINCIDENTAL DISEASES (frequency of occurrence). Neurologic: Neuritis, 5; psychosis, 3; chorea, 3; petit mal epilepsy, 1. Circulatory: Vasomotor instability, 33; emotional hypertension, 7; arterial hypertension, 19; arterial hypotension, 38; myocardial failure, 5; rheumatic mitral disease, 7; syphilitic aortic disease, 1; secondary anemia, 57. Constitutional: Dystrophia dystocia syndrome,[21] 8; Milroy's disease, 1; thyrotoxicosis, 6; myxedema, 1. Urinary: Calculi, 3; nephritis, 6; cystitis, 2. Gastro-intestinal: Irritable spastic colon, 9; peptic ulcer, 2. Infections: Rheumatic infection, 15; tuberculosis, 4; all other infections, 17.

Comment.—The above data demonstrate that the migraine physique is characteristic and should be recognized readily and early. The significant characteristics of the hair, eyes, skin, facies and extremities occur with notable frequency in migrainous individuals. It is an extremely common occurrence that patients with migraine do not volunteer information concerning their attacks. They have had these attacks for years, their mothers before them were similarly afflicted, and they have come to feel that nothing can be done. Because of the continuous apokamnosis or sense of exhaustion and fatigue, ambition becomes dulled and not infrequently a profound belief in constitutional inferiority is of the greatest importance. The intellectual level, however, usually is very high.

Aside from the obvious visible and anatomic findings, some of the physiologic characteristics and consequences deserve comment. Perhaps most significant of these is an undue vasomotor instability.[22] The frequent hypotension, the disturbed peripheral circulation as manifested by pallor and cold, moist extremities, and the high inci-

* Allen[20] reports that the ratio of men to women suffering from migraine is about 1 to 21; Draper[13] reports 1 to 7.

dence of paroxysmal tachycardia illustrate some ill-defined but quite obvious constitutional defect in the equilibratory mechanism of the circulatory system. Local circulatory phenomena are often exaggerated. These patients blush readily and excessively, emotional hypertension is not uncommon[17] and vasomotor coryza is frequent. Along with the instability of the circulatory tonus is an emotional instability which is most frequently manifest as depression. If the theory that the acute migraine attack is due to some form of cerebral arteriolar spasm is a correct conception, such constitutional vasomotor instability as herein described would most certainly be a predisposing factor.

Of the greatest importance in understanding the problems of migraine is an appreciation of the significance of habitual fatigue. This apokamnosis is a very real and major problem to the patient, although there may be but negligible objective evidence thereof. Amelioration of this subjective state can do more to improve the morale and happiness of the patient with severe migraine than anything else. The continuous persistence of this subjective languor is destructive to ambition. Habitual anemia, hypotension,[18] the fatiguing effects of glare[10] on the poorly protected retinæ and many other factors contribute to the maintenance of this state. Furthermore, we may postulate that these individuals are constitutionally decidedly less resistant to the effects of fatigue than normal persons.

Fatigue may be of various types and origin—physical fatigue, as exemplified by the effects of muscular work; mental or emotional fatigue from excessive or prolonged activity (viz., worry),[23] and also the ill-defined fatigue which follows infectious processes or intoxications. This latter is a more generalized disturbance. It is perhaps most characteristically illustrated by the well-known postinfluenzal asthenia. This state of body depletion, exhaustion and vasomotor instability which persists after an influenzal infection closely resembles the habitual state of many migraine patients. One patient defined the condition as "that limp, wet dish-rag feeling." In postinfluenzal asthenia, as in the migraine constitution, the arterial tension is low,[18] the pulse is rapid, there is frequently undue perspiration, especially of the cold extremities, the patient feels weak and exhausted, and mental as well as physical effort is avoided. The situation is not merely a neurocirculatory asthenia,[12] in which the disturbances become manifest only under condition of stress, but resembles a profound generalized change, such as occurs early in convalescence from an infectious disease or a state of habitual intoxication from some noxa as yet unknown.

The relatively high resistance to acute infections in these patients is of great interest. Acute upper respiratory tract infections are very rare, and with the exception of rheumatic infections, other infectious diseases are unusual. The relationship, if any, of the

relatively frequent finding of rheumatic infection or its effects, with the circulatory instability, warrants further study.[16] Along with this relative immunity to transient acute infections, there occurs a notable thermostability. Patients of the typical migraine physique rarely reveal fever during their infections. If fever does appear, it is of lesser magnitude than one would anticipate from the other evidences of infection. It is important that this fact be given consideration in evaluating the significance of the temperature curve in such problems as suspected or early tuberculosis, pyuria, bronchitis, and the like. The absence of fever, or the appearance of but a negligible degree thereof, may be misleading unless one appreciates this unusual thermostability. As yet, we have no clue whatever to the mechanism of these two phenomena—the relative freedom from acute infections, and distinctly more marked thermostability. There is also no evidence indicating whether or not these two characteristics bear any fundamental relationship to one another.

Conclusions. Migraine, long known to be hereditary and, at least in part, of constitutional origin, is very frequently found in persons revealing a characteristic physique or habitat. The more significant structural characteristics are as follows: (1) Very fine, delicate, straight hair, usually brunette; (2) a fine, transparent, childlike skin; (3) unduly large pupils which react normally to light and accommodation; (4) classical, finely moulded features, with narrow nostrils; (5) cold, moist extremities.

This complex, once seen, is readily recognized and is found associated with migraine with great frequency.

The physiologic characteristics are: (1) An unusual degree of vasomotor instability; (2) a markedly lowered resistance to fatigue and, therefore, an habitual apokamnosis; (3) a distinctly increased thermostability; (4) relative freedom from acute infections.

These various characteristics appear with such regularity in patients with migraine that one may justifiably regard them as composing a constitutional type. For this type, for want of a better term, we suggest the term "migraine physique." Recognition of this type does much to clarify some of the problems of migraine. The riddle of migraine is far from being solved, but it is hoped that further study of these interesting constitutional characteristics may be a forward step.

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RINGWORM OF THE SCALP.

CURABILITY, WITHOUT DEPILATING MEASURES, OF INFECTIONS CAUSED BY "ANIMAL" MICROSPORONS.

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ROENTGEN RAY therapy, in epilating dosage, is still frequently used in the treatment of tinea capitis in the Eastern United States. In a number of New York institutions it is carried out as a routine procedure. Epilation by means of the thallium salts is not as popular as the former remedy due largely to the toxic results sometimes produced. Both measures require careful preparation of the patient, elimination of unsuitable patients and meticulous attention to the details of the procedure. Both measures also involve a certain amount of risk to the patient, and accidents, while uncommon, are not unknown. In other sections of the country, epilation by means of Roentgen rays or the thallium salts is also frequently practised, but apparently they are not used to a wide extent in the Southern and Western United States where the local application of medicaments is often sufficient to effect a cure. Mook[1] stated that in St. Louis, ringworm of the scalp invariably responded within 3 to 6 weeks to the local application of such remedies as tincture of iodin,

5% ammoniated mercury ointment, or a salve containing 4% salicylic acid and 8% precipitated sulphur. In 29 years, he had only encountered 2 cases (in brothers) where it was necessary to employ Roentgen epilation.

The advantage of curing the disease through the use of topical remedies rather than Roentgen rays or thallium is probably acknowledged by all, but the numerous remedies advocated (which may be found in any standard text on Dermatology), attest to the relative lack of specificity and uncertainty of cure. The search for a specific cure for tinea capitis has been pursued for many years. MacKenna[2] commented that "from time to time some new form of treatment or some modification of an old one is acclaimed as rapid, efficacious and certain. Long experience and the trial of some of these vaunted quick cures has driven me to the painful conclusion that their enthusiastic sponsors are usually youthful optimists who examine their patients with the eye of faith rather than the lens of the microscope." Ormsby stated that "the indication for the relief of trichophytosis capitis is the destruction of the parasite, and there can be no question that this can be accomplished in some cases without having recourse to epilation." This latter opinion appears to be generally held although the indications for the use of depilating measures or the institution of local therapy is not well defined in any of numerous texts consulted. Of the more recent remedies brought forward, certain volatile oils, first shown to have active antifungicidal properties by Myers,[4] and Kingery and Adkinson,[5] were favorably reported upon in a clinical study by Kingery.[6] Loomis,[7] however, was unable to duplicate his results in a series of patients in Cleveland.

The tendency to biologic cure in certain cases of tinea capitis was emphasized in a recent communication.[8] In such cases, "animal" fungi appear to be the usual causal organisms. The fact that in general, cases due to "animal" organisms are easier to cure than the ones in the M. audouini group, has been mentioned,[9] but has apparently escaped attention in this country or has not been widely accepted. In order to ascertain the effect, if any, the type of fungus present had on the curability of tinea capitis by the use of topical remedies, a series of patients was treated during the past year. The results are given below.

Forty-nine patients with tinea capitis (including favus) were studied, representing the casual applicant to the dispensary in the service of Dr. Fred Wise and cases from other institutions, and in the private practices of coöperating colleagues, among whom should be mentioned Drs. Van Alstyne H. Cornell, E. A. Abbey, G. Astrachan, and P. S. Kerr. The types of fungi grown, and the incidence follow: M. audouini 22; M. lanosum 17; A. schoenleinii 3; Tr. violaceum 1; M. felineum 1; no growth 4; undiagnosed 1. Of this number, 37 cases form the basis of this report. The remain-

der (12 cases) either did not continue under observation, or their exact status was undetermined. Laxity in carrying out the treatment was not deemed sufficient reason for excluding several cases since this was not confined to any one group. The 37 cases herewith reported fell into the following types: M. audouini (20 cases); M. lanosum (12 cases); A. schoenleinii (3 cases); Tr. violaceum (1 case); M. felinium (1 case).

Clinical Data. An analysis of the patients revealed 28 males (75%) and 9 females (25%).* The average age of all the patients was $7\frac{1}{4}$ years. The youngest was $3\frac{1}{2}$ years and the oldest 17 (case of favus). The duration of the disease varied considerably according to the organism isolated. In patients from which M. lanosum was cultured, the disease was present less than 3 months on the average, varying in individuals from 3 weeks to 6 months. In the M. felineum case, the duration was said to be 1 week. In the M. audouini cases, the average duration was $8\frac{2}{3}$ months, varying in individual cases from 2 months to 2 years. In the 3 cases of favus, the infection had been present for $1\frac{1}{2}$, 2 and 3 years respectively. The patient from which Tr. violaceum was isolated stated that the disease was first noticed 5 years before. To 5 patients (3 M. lanosum; 1 M. audouini and 1 A. schoenleinii) Roentgen ray epilation had previously been given. Most of the cases due to an "animal" microsporon, exhibited more inflammatory reaction than the others, although in 3 such cases no erythema was noted and the infections were considered on clinical grounds to be due to M. audouini, bearing out the assumption that a botanical diagnosis is not always possible from the clinical characteristics. No typical kerions were present in any case but in several instances, pustulation was noted.

Wood Light. In addition to microscopic and cultural studies, hairs either *in situ* or after removal, were examined under the Wood light.† With the exception of 1 case, in which a spontaneous cure apparently occurred, fluorescence of the infected hairs was observed. In all the microsporon infections, the well known bright green effect was noted. In favus, some difficulty was usually met with in distinguishing the infected hairs, which however, on careful examination, could be usually singled out as showing in their entirety, a lighter hue than the normal hairs present and usually fluorescing

* A review of 108 consecutive cases from the Skin Clinic revealed the incidence between the sexes to be 80 males (77%) and 28 females (23%). Crocker[10] stated that in 600 cases, the disease was 6% more prevalent in boys. Beeson[11] noted that 85% of his cases were males. In Pardo-Castello's series,[12] there was only 1 girl to 31 boys. In this connection it is interesting to note that in ringworm of the adult scalp, Fox and Fowlkes[13] found that in 48 collected cases, 32 females were affected (66%).

† The Wood filter is composed essentially of nickel oxid; the best glass according to Radley and Grant[14] contains 9% of the salt together with silica, barium oxid, potassium oxid and copper oxid. When a source of ultraviolet light is screened with this glass, all the visible rays are absorbed while the ultraviolet rays are transmitted through the filter. Many substances when exposed to the rays, in a dark room, fluoresce in a characteristic fashion.

near the scalp but not with the brilliance of the microsporons. The infected hairs in the case of the Tr. violaceum infection showed a bluish-white color not noted in the other varieties. In appearance it resembled the fluorescence of petrolatum, but was differentiated by the negative history of application of grease and from the observation that not all neighboring hairs showed the fluorescence; these hairs also invariably contained fungous material while those not fluorescing were found to be normal. It appears important to remember that in favus and in many of the endothrix trichophytons the affected hairs are not broken off in short stumps as in the microsporons. Fungous elements usually only invade part of the shaft; consequently only part of the hair fluoresces. However, because of toxic, nutritional or other factors, the remainder of the hair appears lusterless and lighter than normal hair.

The Wood light was an almost indispensable help in determining cure; infected hairs were frequently found when the disease was apparently eradicated to the unaided eye.

Method of Treatment. It was felt desirable to standardize the treatment in order to arrive at a fair comparison in the results. Having in mind the time-honored value of iodin, and impressed with the possibilities of the volatile oils, a prescription was concocted containing iodin crystals, thymol and oil of cinnamon āā 1% in petrolatum. This was found to be slightly irritating. In only 4 cases were different preparations given. In 1 instance, a chlorin compound in petrolatum was used; in another case 1% iodin crystals in petrolatum was prescribed and in 2 instances the treatment consisted of a 10% ammoniated mercury ointment. In all 4 cases, the causal fungus was M. lanosum. The parents or attendants were instructed to apply the medicament twice daily preceded by a soap and water shampoo. No manual epilation was practised. The usual hygienic precautions were also outlined. Shaving or clipping of the hair was not stressed although in some instances this was done to facilitate the treatment. The patients were reëxamined as frequently as possible and the clinical impression was checked by the Wood light and microscopic and cultural determinations.

Results. The uniformity of the results was surprising. All 12 cases due to M. lanosum and the case due to M. felineum were cured, whereas in none of the cases due to M. audouini, A. schoenleinii, or Tr. violaceum (24 cases in all) was the disease eradicated. Another patient (not included in this series) spontaneously recovered from an obvious ringworm infection of the scalp; no fungi were demonstrated from the scalp but a coincident tinea circinata of the neck revealed M. lanosum. The cases in the M. lanosum group were cured on an average of just under 2 months, the shortest time being 3 weeks and the longest time being 3 months. The 4 cases treated with compounds other than the standard formula, all

responded favorably in approximately the average time required for the others. In the case of the patient treated with the chlorin compound, her brother received the standard treatment and both were discharged as cured at the same time. Treatment in the cases due to M. audouini was pursued for an average time of 3½ months, the shortest time being 3 months and longest 5 months. The favus cases were treated for 2, 5½ and 8 months and the case due to Tr. violaceum for 5 months.

Comments. The reason for the favorable outcome in the one group is not known. The effect may be due to irritation causing inflammatory changes finally resulting in a biologic cure. Against the premise of a direct fungicidal action was the success achieved in 4 cases of "animal" infection, using different remedies; the failure to cure when other fungi were involved would also speak against a specific medicinal effect.

The lack of response to treatment in the latter group, does not necessarily preclude the possibility of cure without resort to the use of Roentgen rays or thallium acetate. Other remedies and the use of mechanical epilation might be effective, especially when active coöperation of the parents is obtained. There is reason to believe that many such cases have been cured in the past. The results of this investigation, however, indicate a decided difference in the response to therapy between the different species. While no ectothrix (animal) trichophytons were included in this study, it is likely that they also might react favorably to local therapy. Although the results here recorded were uniformly successful insofar as the "animal" microsporons were concerned, the series of cases is too small to state with certainty that all such cases would similarly respond. It is also suggested that reports showing good results from the use of certain drugs applied locally may be justly criticized if cultural studies are lacking, since the favorable outcome might only in part be due to the therapy. Cultural determination of the causative fungus is rarely a routine procedure prior to the treatment of tinea capitis, even in many of the larger institutions. The demonstration of fungi in extemporaneous preparations is usually considered sufficient evidence to proceed with therapy. From the evidence submitted in this report, determinative mycology would appear to be of value from a practical standpoint in treating tinea capitis; *i. e.*, cultures must be obtained!

Incidence of "Animal" Microsporon Infection. The mycologic flora appears to vary considerably in different parts of the world.[15] Walker[16] noted the preponderance of microsporon infection in Tinea capitis in Scotland and England while in Italy the trichophytons were chiefly responsible. The "animal" microsporons would appear to be negligible in the British Isles. Sabouraud's statistics[17] reveal that only 3% of his cases were due to M. lanosum and a recent report[18] from Bordeaux failed to reveal any "animal" microsporons

in an analysis of 176 patients. Very few complete studies appear to have been made in the United States and Canada (Table 1). Wise[27] stated that 20 years ago, the cases in New York were preponderantly of the non-inflammatory type, considered to be M. audouini infections. The situation today has apparently changed although the cases found in institutions or orphan asylums are still usually M. audouini infections. In the patients comprising the series herewith reported, the disease was caused by "animal" microsporons in 13 out of 37 cases (35%). This figure, however, is misleading insofar as the ordinary run-of-case in the dispensary is concerned, since only 3 of the M. audouini cases should be so included. Excluding institutional cases, it was found that in 65% of the cases the infections were due to "animal" microsporons. It would thus appear likely that a fair percentage of cases of ringworm of the scalp throughout the country are caused by "animal" microsporons.

TABLE 1.—INCIDENCE OF FUNGUS SPECIES CAUSING TINEA CAPITIS IN THE UNITED STATES AND CANADA.

Authority.	Location.	Number of cases.	Microsporon audouini (human type).	Microsporon lanosum; Microsporon felineum (animal types).	Other species.
White[19]	Boston				
Corlett[20]	Cleveland	M. audouini stated to be the predominant organism.			
Wende[20]	Buffalo				
Beeson[11]	Chicago				
Greenwood[21]	Boston	40	25.0%	67.5%	7.5%
Burgess[22]	Montreal	62	32.2%	33.9%	33.9%
Pardo-Castello[12]	Havana	32	.....	100.0%	
Davidson and Gregory[23]	Winnipeg	75	57.0%	43.0%	
Mook[1]	St. Louis	Majority of cases acquired from animals.			
Weidman[24]	Philadelphia	36	41.7%	50.0%	8.3%
Jacobson[25]	Los Angeles	..	.....	Most frequent	
Smith[26]	El Paso	..	rarely found		

Summary and Conclusions. 1. Thirty-seven patients with Tinea capitis were treated with local applications only (*i. e.*, without depilating measures).

2. The results were uniformly good in 13 cases in which the causal fungi were "animal" microsporons.

3. Twenty-four other cases due to M. audouini, A. schoenleinii and Tr. violaceum failed to respond to similar treatment.

4. The ointment used by the majority of the patients in this series is not advanced as a "specific cure" for the cases which responded favorably; it is more than likely that the medicament used might vary considerably in its composition and still be used

successfully in the treatment of infections due to "animal" microsporons.

5. The results of this investigation point to an explanation for the discrepancies in the results which might occur when a given formula is used by different observers in different sections of the country. Likewise, the experience of a physician whose cases are mainly institutional might differ from one whose patients are seen in the dispensary or in private practice, since ringworm of the scalp in orphan asylums and the like is mainly due to M. audouini while M. lanosum is responsible for a considerable percentage of the latter.

6. Tinea capitis, when caused by "animal" fungi, is shown to be curable by local therapy alone in from 3 to 12 weeks. It is suggested that cases in this category should be segregated, for treatment, from the more resistant forms which might require depilating measures by means of the Roentgen rays or thallium acetate. *Cultural determination of the causative fungus would thus appear highly desirable and of practical importance in the management of ringworm of the scalp.*

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THE ALLEGED INCREASE OF SENSITIVITY OF VASCULAR RESPONSE TO EPINEPHRIN FOLLOWING INJECTION OF PLASMA FROM NEPHRITIC PATIENTS.

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Investigations by Hülse,[1] in Volhard's Clinic, appear to demonstrate that the elevation of blood pressure in patients suffering from nephritis is due to the occurrence of a peptone-like substance in the blood. This substance was found in serum by two methods. The first consisted in the injection of serum into animals and the demonstration that such animals were more sensitive to the pressor action of epinephrin than before treatment with serum. Serum of normal subjects or of patients with essential hypertension did not exhibit this "sensitizing" action. The second method (Hülse and Strauss[2]) consisted in the demonstration that the protein-free trichloracetic acid filtrate of blood from hypertensive patients with nephritis invariably exhibited an increase in the formalin titrable amino-N after acid hydrolysis (bound amino-N). From these results it was concluded that peptone-like substances appear in the blood of such patients and that it was this fraction which caused the sensitizing action for epinephrin. Neither normal persons nor patients with essential hypertension exhibited any increase in bound amino-N.

The result of the latter of these two methods for demonstrating sensitizing substances has recently been shown to be incorrect by both Jackson, Sherwood and Moore,[3] and more recently by Becker and Herrmann.[4] Neither group of investigators was able to find any relationship between the bound amino-N and the height of the blood pressure.

The biological experiments, however, still remained unquestioned. As the problem is one of importance to the understanding of the mechanism of hypertension, we have thought it desirable to attempt to confirm or disprove Hülse's contention.

Method. Most of our experiments were conducted on pithed cats because of their very high sensitivity to epinephrin. The animals were quickly anesthetized with ether, the vagus nerves cut and a tracheal cannula inserted. Blood pressure was recorded by a mercury manometer from the carotid or femoral artery. The skull was trephined and the brain and cord destroyed. Artificial respiration was immediately instituted and no more anesthetic administered. Doses of 1 to 2 cc. of 1 to 2,000,000 epinephrin solution were injected into a femoral vein as soon as the blood pressure had reached a constant level. After repeating the injections a number of times (requiring about ½ to ¾ hour after discontinuing the ether),

10 to 20 cc. of warm fresh heparinized plasma was slowly injected. The plasma was usually ready for injection 5 to 10 minutes after withdrawal from the patient. Directly following the plasma injection, epinephrin doses were again administered. In some experiments pitressin was then injected in order to enhance the sensitivity of the animal to epinephrin. Just enough was given to produce a very slight rise in the level of blood pressure, and when the pressure had again fallen nearly to normal, epinephrin was again given.

Experiments were also performed as outlined, but employing etherized cats with the central nervous systems intact.

Besides native plasma, alcohol extracts of plasma were prepared by a method published elsewhere.[5] It consisted in precipitation of proteins and lipids with alcohol, removal of the alcohol under vacuum and freezing the remaining fat from the extract. A clear water extract of the plasma resulted. Ultrafiltrates of plasma were also prepared by three different methods: (1) Dialysis through collodion thimbles. (2) Suction through collodion coated porcelain pear-shaped thimbles. (3) High pressure filtration. (Pfaltz and Bauer apparatus.)

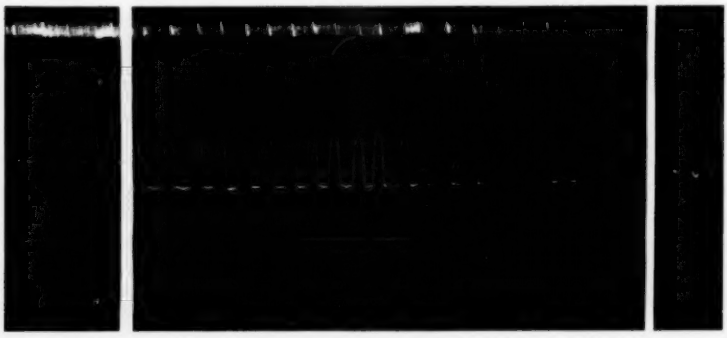

FIG. 1.—Example of the progressive increase in response of the pithed cat to injections of 2 cc. of 1 to 200,000 epinephrin. Ether removed 45 minutes before the injections were begun. Initial pressure, 62 mm. Hg.

RESULTS. Repeated injection of epinephrin into pithed cats led to a progressive increase in the vascular response to it (Fig. 1). This action of epinephrin was first noted by Lévy[6] and has been studied in detail by Weyman and Lutz.[7] Animals with intact nervous systems also exhibit the phenomenon (Fig. 2). It is, therefore, evident that any increase in sensitivity must be corrected by subtraction of the increment which normally accompanies repeated injections of epinephrin. This Hülse did not do.

In no experiment (22 experiments) did we observe an increase in the sensitivity of the pithed animal to epinephrin following the intravenous injection of from 10 to 20 cc. of plasma, whether the plasma originated from patients with severe nephritic hypertension (8), essential hypertension (6) or normal subjects (3). Negative results were also obtained on animals in which the central nervous system was intact.

Administration of pitressin increases the sensitivity of the animal to epinephrin two to fourfold. In those animals with enhanced susceptibility, administration of plasma was also unsuccessful in

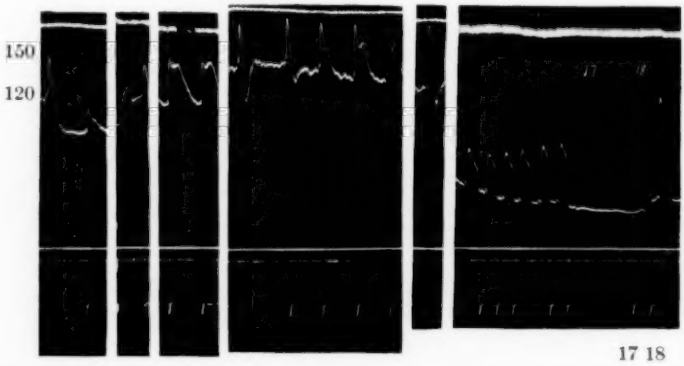

FIG. 2.—Sensitization to epinephrin with and without central nervous system intact. Repeated injections of 2 cc. of 1 to 100,000 epinephrin. At 17, extract of 20 cc. plasma of a severe hypertensive nephritic (blood-pressure, 216/126) was injected. At 18, a small dose (1 cc. of 1 to 25 dilution) of pitressin was given, followed by the usual epinephrin dose. Initial pressure, 120 mm. Hg.

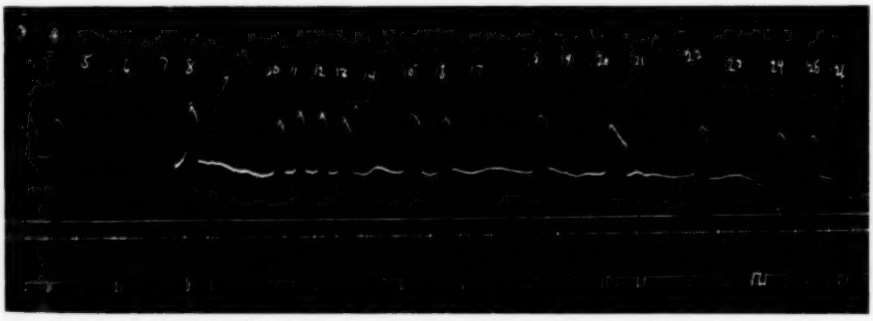

FIG. 3.—Sensitivity to epinephrin following plasma and plasma extract injection in pithed cat. 3, 4, 2 cc. of 1 to 100,000 epinephrin. 5, Extract of 5 cc. plasma of severe nephritic with hypertension (blood-pressure, 200/122). 6, Extract of 30 cc. plasma of same patient. 7 and 8, Epinephrin. 9, Extract of 15 cc. plasma from same patient. 10 to 13, Epinephrin. 14, 10 cc. plasma from same patient. 15 and 16, Epinephrin. 17, 10 cc. plasma from same patient. 18, Epinephrin. 19, Extract of 15 cc. plasma from same patient. 20, Epinephrin. 21, Extract of 20 cc. of plasma from severe essential hypertensive (blood-pressure, 220/130). 22, Epinephrin. 23, Extract of 20 cc. plasma from nephritic without hypertension (blood-pressure, 120/60). 24 and 25, Epinephrin. 26, Extract of 18 cc. plasma from severe essential hypertensive Expt. No. 110 (blood-pressure, 52 mm. Hg.).

further increasing it. Neither did ultrafiltrates (9) nor alcoholic extracts (19) of plasma exhibit the slightest effect on epinephrin susceptibility (Fig. 3) regardless of the origin of the plasma.

Discussion. Native plasma, alcoholic extracts and ultrafiltrates thereof do not alter the responsiveness of the vascular system to epinephrin either in pithed cats or etherized normal cats. We, therefore, find no basis for Hülse's claim that substances which enhance the vascular action of epinephrin are present in the blood of hypertensive nephritic patients. It is possible that he mistook the increased susceptibility to epinephrin which normally accompanies its repeated administration for an effect due to plasma.

These experiments appear to remove the support which the pharmacologic method offered to Hülse's theory of hypertension. We have already referred to the fact that Hülse and Strauss'[2] chemical evidence as to the existence of peptone in the blood of hypertensive nephritic patients has not received confirmation by other investigators.[3,4]

Conclusions. Hülse's theory that the hypertension in nephritis is due to occurrence of peptone-like substances in the blood which are able to sensitize the bloodvessels of animals to epinephrin receives no support from this investigation. It was shown that heparinized plasma, ultrafiltrates and alcohol extracts thereof do not increase the vascular response of cats to epinephrin regardless of whether the plasma originates from patients with nephritis, with hypertension, essential hypertension or normal subjects.

Epinephrin repeatedly injected normally increases the vascular response of anesthetized animals to it. This fact may partially explain Hülse's results.

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A NOTE ON PARENTERAL LIVER THERAPY IN STREPTOCOCCUS PNEUMONIA.

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Liver extract injected intramuscularly and intravenously causes a leukocytosis and a relative increase in the neutrophils. This was shown by Foran, Sheaff and Trimmer[1] in the successful treatment of 5 cases of agranulocytic angina. Murphy[2] reported finding a leukocytosis, as well as an increase in hemoglobin and erythrocytes, in pernicious anemia following injections of liver extract.

Meyer, Middleton and Thewlis[3] studied 4 apparently normal persons and 3 with abnormal conditions. Injections of liver were given, then frequent white blood counts made. In all, there was a definite increase in the white blood cells. In 1 case, the leukocyte count increased following the injections of liver extract, before and after splenectomy. They conclude that parenteral liver extract stimulates the bone marrow and other sources of the cellular elements of the blood.

Middleton and Gibbon[4] in a study of 164 cases of pneumonia in hospital practice, 64 of which died and 100 recovered, found the average leukocyte count of the recovered cases was 21,046, and of those who died 14,700. They expressed the opinion that the absence of leukocytosis is unfavorable, and leukopenia an ominous sign in pneumonia. A high total leukocyte count, especially 20,000 or above, is reassuring.

It seems reasonable, therefore, to expect that in view of the published data on the effect of liver therapy on leukopoiesis, it would be of value in cases of pneumonia with leukopenia or low leukocyte count. The object of this report is to place on record a description of 2 cases of streptococcus lobar pneumonia which showed striking improvement following parenteral liver therapy.

Case Abstracts. Case 1.—R. F., aged 45, Swedish-American, milk dealer and farmer, had previous attacks of pneumonia in 1920 and 1926. Family history negative, except that father and mother, on adjoining farm, were just recovering from pneumonia. He was first seen at his home, February 6, 1934, complaining of general malaise, fever and pains in the right chest. Many fine râles were heard in the right axilla. Leukocyte count was 16,000 (Table 1). On the morning of February 9, he was definitely worse, very toxic, coughing a small amount of bloody sputum, and was admitted to the Meriden Hospital. The next day, the fifth day of his illness, he was gravely ill, irrational, and with a lowered leukocyte count. That afternoon, liver injections were started, and by the end of the sixth day, he was definitely better and continued to improve. His temperature receded by lysis, reaching normal on the eleventh day.

Physical Examination. A very well nourished, adult, white male, slightly confused mentally. Respirations were rapid, skin flushed and cyanotic. Chest showed definite pneumonia with many fine crepitant râles in the right axillary region. Heart sounds were fast but normal. Abdomen was slightly distended.

Laboratory Examination. Blood counts (Table 1). Sputum was bright red and on direct smear showed long chains of streptococci. Cultures on blood agar showed Beta hemolysis. Negative for Type I, II, III and VII pneumococci (Neufeld). Urine, 1.023, negative albumin and sugar, rare red blood cell. Report of Roentgen ray taken the twelfth day showed consolidation of the upper and middle lobe of the right lung undergoing resolution. No fluid present.

Treatment. Oxygen therapy was started on the third day and given through the seventh day. Liver extract injections (intramuscular) were started on the fifth day of the disease. Ammonium chlorid was given in small doses in the beginning; and on the fifth and sixth days, Digalen (Roche) and strychnin were given hypodermically to support the circulatory system.

TABLE 1.—BLOOD FINDINGS.

Case 1.

Date.		Liver extract (cc.)	W. B. C. in thousands.	Polymor.	Temp.	Urine 24 hours (in cc.).
2- 7-1934			16.0	91%	103°	
2- 9-1934			9.2	88	104	1600
2-10-1934	9 A.M.		8.2		103.6	500
	4 P.M.	3				
	10 P.M.	3				
2-11-1934	5 A.M.	3				3400
	9 A.M.		27.8		102	
	10 A.M.	3				
	3 P.M.		25.4			
	10 P.M.	4				
2-12-1934			26.8	84	101	1050
2-13-1934			25.0		100.2	1300
2-14-1934			24.4		100	950
2-15-1934			20.0		100	1750

1 cc. is equivalent to 50 gm. of fresh liver (Endo).

Case 2.

7-17-1934			10.4	75%	104.2°	700
7-18-1934			8.2	72	104	300
7-19-1934	10 A.M.	2	5.2	68	105	600
	4 P.M.		7.2	67		
	10 P.M.	2				
7-20-1934	9 A.M.		6.8	70	105.4	850
	10 A.M.	4				
	10 P.M.	4				
7-21-1934	10 A.M.	4	6.4	67	104.2	1000
7-22-1934	10 A.M.	4			104.4	700
7-23-1934	10 A.M.	4	7.2		103.8	1050
7-24-1934			8.4		103	1450
7-26-1934	10 A.M.		4.6		102.6	1500
7-27-1934	10 A.M.	4			100.2	1350
7-28-1934			12.2		99.6	
8- 1-1934			7.2	68	98.8	

CASE 2.—W. L., aged 21, graduate nurse, family and personal history negative, was taken ill on July 15, 1934, and admitted to the hospital on the third day of her illness, complaining of general malaise, fever and slight cough. The fourth day, a Roentgen ray of her chest revealed a pneumonic process in the left outer middle area. No physical signs were present until the seventh day when many fine râles were heard over the same area. Temperature ranged from 101° F. in morning to 105.4° F. in afternoon, the highest point being reached on the sixth day. Her temperature gradually receded with improvement in her general condition, and on the fifteenth day, the temperature was normal.

Physical Examination. Patient slightly built, poorly nourished, mentally clear, no dyspnea or cyanosis. Face was flushed, throat slightly reddened, lungs clear, no râles heard. Heart sounds were regular, systolic murmur at the apex. This was an old lesion and had been noted 3 years before this illness. Abdomen and extremities were normal.

Laboratory Examination. Blood counts (Table 1). Sputum was scanty in amount, yellow, negative for tubercle bacilli and for Type I, II, III and VII pneumococci (Neufeld). Direct smear showed many long chains of streptococci. Cultures on blood agar showed Beta hemolysis. Blood Wassermann was negative. Agglutination tests of blood serum were negative for typhoid, paratyphoid A and B, Weil-Felix and undulant fever.

Treatment. Ammonium chlorid in small doses. Liver extract injected daily from the fifth to the ninth days inclusive and again on the twelfth day (see table).

Discussion. The injection of liver extract was tried in the first case of pneumonia because of the drop in leukocyte count from 16,000 to 8200 in 3 days. When liver extract was started, this patient was seriously ill, in a light stupor, high fever, able to take very little nourishment, and voided 500 cc. of urine in 24 hours. The prognosis seemed poor. Sixteen cc. of liver extract (equivalent of 800 gm. of fresh liver) were given intramuscularly between 4 P.M. of the fifth day and 4 P.M. of the sixth. The leukocyte count rose from 8200 to 27,800. The patient improved. He voided 3400 cc. of urine in 24 hours, and although still confused mentally, the stupor was less and the fever lower. The leukocytes remained above 20,000 until the tenth day of his illness. The fever came down by lysis and there were no complications. He was discharged from the hospital on the fifteenth day.

The leukocyte count in the second case, on the third day of illness was 10,400 and had dropped to 5200 on the fifth day. Daily liver extract injections were started on the fifth day and given for 5 days. The general condition of the patient was greatly improved, and the average leukocyte count was 7000. No injections were given on the tenth, eleventh and twelfth days of the disease. The leukocyte count on the twelfth day was 4600. Four cc. of liver extract were given on the thirteenth day, and on the fourteenth day, the count rose to 12,200. In 3 more days the count dropped to 7000. The temperature was normal by this time, the patient improved rapidly and no complications occurred.

Differential counts coincided with the number of leukocytes. An increased leukocyte count was accompanied by a relative increase in the neutrophils. The number of white blood cells seemed to be a sufficient index of the patient's condition.

The diagnosis of streptococcus pneumonia was based on the report of large numbers of streptococci in the smears and cultures from the sputum and the negative result for pneumococcus Types I, II, III and VII and the absence of pneumococci in smears of sputum. The sputum in one case contained bright red blood and in the other it was yellow. In neither was it the typical rusty or brown sputum characteristic of a pneumococcal infection.

In studying the hospital chart, it was interesting to note that the output of urine was below normal just before the liver therapy was instituted, and greatly increased after it was given in each case (see table). The first patient averaged an intake of 3000 cc. of fluids a day and the second 2500 cc. daily.

Summary. 1. The effect of parenteral liver extract in the 2 cases of streptococcus lobar pneumonia described, suggests that it is a valuable therapeutic agent. Recovery took place in both cases

with no complications, the temperature returning to normal by lysis.

2. Due to the success of liver therapy in these cases, it should be considered in any type of pneumonia with a low or receding leukocyte count.

3. Daily or frequent leukocyte counts are important indices in the progress of a pneumonia patient.

4. The daily output of urine was increased following the liver treatment.

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THE ETIOLOGY OF "ALCOHOLIC" POLYNEURITIS.*

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Since Lettsom[1] first described "alcoholic" polyneuritis, in 1787, a direct neurotoxic effect of alcohol has been considered to be the causative agent. Six years ago, however, Shattuck[2] suggested that this disease was "caused chiefly by failure to take or to assimilate food containing sufficient quantity of vitamin B" and "might be properly regarded as beriberi." Meyer,[3] Wechsler[4] and a number of other clinicians have concurred in this point of view, without, however, advancing any further evidence for it. Minot, Strauss and Cobb[5] have discussed the subject, pointing out the clinical and pathologic similarities between the polyneuritis associated with alcoholism and that of beriberi, and noting the fact that over one-fourth of their 57 patients with undoubted "alcoholic" polyneuritis also had pellagra, a disease which is now generally believed to be the result of dietary deficiency. Dietary histories of 43 of their patients showed that 41 of these individuals had partaken of grossly inadequate diets for prolonged periods of time. Twenty-one patients had gastric anacidity and 15 had gastric hypoacidity, which states might well have interfered with the proper assimilation of nutriment from the gastro-intestinal tract. While these facts undoubtedly add to the concept that "alcoholic" polyneuritis is

* A preliminary report of this study was presented before the American Society for Clinical Investigation at Atlantic City, N. J., April 30, 1934.

the result of dietary deficiency, they fail to prove the case against a direct neurotoxic effect of alcohol upon peripheral nerves.

The work of Spies and DeWolf[6] on "alcoholic" pellagra suggested that a method similar to theirs might be employed in making observations upon patients with "alcoholic" polyneuritis. If alcohol has a direct neurotoxic effect on peripheral nerves in the amounts consumed by the individuals who develop polyneuritis, then this condition should become progressively worse if the use of alcohol in similar amounts is continued. Certainly no amelioration of the polyneuritis should be expected in patients who continue the excessive use of alcohol.

Procedure. Ten patients with "alcoholic" polyneuritis not complicated by severe febrile infections or decubitus were selected for study. Data concerning these individuals are summarized in Table 1. By careful questioning, the usual daily intake of spirituous liquors was determined in each case. Such an amount of pure blended whisky (from 1 pint to 1 quart) was then administered daily to each patient throughout the period of study. At the same time each patient was placed upon a dietary régime which included 2 eggs, 1 pint of milk, 225 gm. of beef or lamb, 240 cc. of orange juice and 4 servings or about 240 gm. of green vegetables daily, *as a minimum.* Other foods were added to make up the necessary total caloric intake for each individual. Eighteen grams of Vegex, or 30 Harris yeast-vitamin tablets, or 90 gm. of dried brewers' yeast were administered daily by mouth; 10 cc. of solution liver extract, Lilly (N.N.R.),* were injected intramuscularly each week, and 10 cc. of a vitamin B concentrate* were injected intramuscularly daily in each patient.

From evidence in the literature, it appears that neural changes may result from dietary deficiencies other than a lack of vitamin B_1. Mellanby[7] suggests that vitamin A is necessary for the integrity of the nervous system, and Gildea, Kattwinkel and Castle[8] produced neural lesions in dogs by the use of diets deficient in the vitamin B complex. Cowgill *et al.*[9] have reported demyelination of peripheral nerves in dogs deprived only of vitamin B_2 (G) and also in dogs maintained on the Goldberger 195 diet.[10] The occurrence of spinal cord and peripheral nerve lesions in pernicious anemia[11] suggests the possible rôle of a lack of the "liver extract" factor. The influence of malabsorption from the intestinal tract in the production of polyneuritis has recently been reviewed.[12] These facts led to the employment of diets adequate in all respects, and, in addition, to the parenteral administration of both vitamin B concentrates and liver extract.

When this study was commenced it was found that even endless patience and skill on the part of the nursing staff was insufficient to make these patients eat the requisite food, owing to the anorexia

* Kindly supplied by Eli Lilly and Company, Indianapolis, Ind.

TABLE 1.—SUMMARY OF NEUROLOGIC EXAMINATIONS BEFORE AND AFTER TREATMENT WITH HIGH VITAMIN DIET, PARENTERAL VITAMIN B AND LIVER EXTRACT AND LARGE QUANTITIES OF WHISKY UPON 10 PATIENTS WITH "ALCOHOLIC" POLYNEURITIS.

Age and sex of patient	51 yrs., M.		30 yrs., M.		32 yrs., M.		41 yrs., F.		37 yrs., M.		42 yrs., M.		38 yrs., M.		53 yrs., M.		36 yrs., F.		42 yrs., F.	
Duration of polyneuritis (before treatment)	10 weeks		2 weeks		8 mos.		9 weeks		5 mos.		1 week		3 weeks		5 weeks		5 years		9 weeks	
Daily intake of whisky (during treatment)	1 quart		1 quart		1 quart		1 pint		1 pint		1 quart		1 quart		1 pint		1½ pints		1½ pints	
Duration of treatment	33 days		129 days		90 days		63 days		78 days		24 days		14 days		32 days		115 days		63 days	
Time of examination with regard to treatment	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
Strength, arms and hands	− −	N	− −	N	− −	N	− −	N	− −	N	N	N	N	N	N	N	− − − −	N	− − − −	N
Deep reflexes, arms	+	N	N	N	N	N	+ +	N	0	N	N	N	N	N	N	N	− − −	N	+	N
Skin sensation, arms and hands	−	N	− − −	N	N	N	N	N	− − − −	N	N	N	N	N	N	N	− − − −	N	− − − −	N
Vibration sense, ulnæ	−	−	N	N	−	N	−	N	N	N	N	N	N	N	N	N	N	N	− − −	− −
Strength, legs and feet	− −	N	− − −	N	− − − −	N	− − − −	−	− − −	N	−	N	− − −	N	− − −	N	− − −	N	− − − −	N
Knee jerks	N	−	N	−	0	− − − −	0	− − − −	0	0	N	N	− −	N	−	N	0	0	0	− − − −
Ankle jerks	0	0	− − −	− − −	0	0	0	0	0	0	−	N	0	− − − − − − −	− − − − − − −	0	0	0	0	0
Plantar responses	N	N	N	N	0	N	0	N	N	N	N	N	N	N	N	N	0	N	0	N
Skin sensation, legs and feet	− −	N	− − −	−	− − − −	N	− − − −	N	− − − −	N	− − −	N	N	N	− − −	N	− − − −	N	− − − −	N
Position sense, toes	−	N	N	N	0	N	− −	N	N	N	N	N	N	N	N	N	− − − −	− −	− −	N
Vibration sense, tibiæ	0	0	− − −	−	− − −	−	0	N	0	− − −	0	−	−	N	0	0	0	0	0	0
Tenderness of calves	+ + +	N	+ + +	N	+ + + +	N	+ + + +	N	+ + +	N	+ + + +	N	+ + + +	N	+ + + +	N	+ + + +	N	+ + + +	N
Standing*	− −	N	− −	N	0	N	− −	N	− −	N	−	N	N	N	−	N	0	−	0	N
Walking*	− −	N	− −		0		0	N	− −	N	− −	N	− −	N	− −	N	0	− −	0	N
Mental state†	N	N	N	N	N	N	+ +	+	N	N	+	N	N	N	N	N	+ + + +	+ +	+ +	+

N signifies normal. 0 signifies absent. The number of minus or plus signs signifies the degree of diminution or increase, respectively, in the sign.

* When standing or walking are represented by 0, this signifies inability to stand or walk.

† Under mental state is indicated the Korsakow type of psychosis.

so common in "alcoholic" polyneuritis. Accordingly, a decision was made to abandon the study in any individual who would not eat. It was, therefore, made clear to each of the patients that if he did not eat all the food presented, the customary postprandial whisky would not be forthcoming. Need to carry out this threat occurred but once during the course of the 1918 meals served to the 10 patients.

Results. The results obtained during the period of observation are summarized in Table 1. Examination of this data shows that, without exception, the polyneuritis of each of the 10 patients was improved during the constant administration of large amounts of whisky. Clinical observation of these individuals revealed no differences in the rapidity or degree of recovery of the polyneuritis as compared to similar patients treated without whisky.

Discussion. It is apparent from the above that ingestion of alcohol had no demonstrable neurotoxic effect on peripheral nerves when given in amounts up to a quart a day, in patients who were partaking of an adequate diet and receiving injections of liver extract and vitamin B concentrates. Nevertheless, it remains theoretically possible that even smaller quantities of alcohol so administered as to raise the blood alcohol to a high concentration might cause damage to the peripheral nerves. It is a matter of commonplace observation that a pint of whisky ingested at one time on an empty stomach will produce cerebral effects far in excess of those caused by twice that quantity of alcohol ingested in frequent small amounts over a period of many hours. However, polyneuritis has not been reported following acute alcoholism except when a definite poison such as triorthocresyl phosphate[13] has been ingested with the alcohol, in which case the clinical features of the polyneuritis are quite different from those of the polyneuritis associated with chronic alcoholism. Furthermore, "alcoholic" polyneuritis has not been encountered, at least in recent years, among a university group of about 7500 young men, some of whom, there is reason to believe, not infrequently ingest excessive quantities of alcohol during such a relatively short period of time that marked cerebral effects are produced, including unconsciousness.*

Many years ago, Eijkman[14] suggested that foods such as polished rice, being overrich in starch, produced a substance in the intestine which was poisonous to nerve cells and for which the outer layers of rice acted as an antidote. One may similarly argue today that alcohol is poisonous to nerve cells unless there is a sufficient amount of vitamin B or some other dietary factor present to act as an antidote. Such speculation must remain unanswered for the present.

The observations reported here do not in any way eliminate the possibility that some impurity which might have been present in

* Personal communications from the various physicians in charge of the health of this group of young men.

the beverage alcohol consumed by these patients before the onset of polyneuritis was responsible for the nerve lesions. However, the data presented clearly indicate that the administration of pure blended whisky in quantities varying from 1 pint to 1 quart daily in no way prevents the relief of "alcoholic" polyneuritis when the patients are adequately nourished.

The clinical and pathologic aspects of the polyneuritis associated with alcoholism are essentially the same as those of the polyneuritis of beriberi. The dietary histories of the patients and the common association with easily recognizable deficiency diseases, such as pellagra, make it appear probable that "alcoholic" polyneuritis is a dietary deficiency disease similar to beriberi. The high incidence of gastric secretory defects in these patients suggests that poor assimilation of nutriment from the gastro-intestinal tract plays a rôle in conditioning the deficiency state.

Summary and Conclusions. Ten patients suffering from "alcoholic" polyneuritis were allowed to continue their customary daily intake of spirituous liquor on condition that they consumed a well-balanced, high vitamin diet supplemented with yeast or its products. They were further given vitamin B concentrates and liver extract by parenteral injection in order to obviate any possible disturbance in absorption present in the patients or resulting from their use of alcohol. Improvement in the polyneuritis occurred in every instance.

The conclusion is drawn that "alcoholic" polyneuritis does not result primarily from a direct neurotoxic effect of alcohol, but is probably the result of a dietary deficiency, possibly conditioned in some cases by disturbed gastro-intestinal function. "Alcoholic" polyneuritis may be regarded as similar to the polyneuritis of beriberi and treated accordingly.

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SEDIMENTATION TIME AS AN AID IN DIFFERENTIATING ACUTE APPENDICITIS AND ACUTE SALPINGITIS.

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The rapid sedimentation of erythrocytes has been observed in inflammatory diseases. As a diagnostic aid in differentiating these diseases, the consensus of opinion is that it offers nothing more than the leukocyte and differential counts.[1]

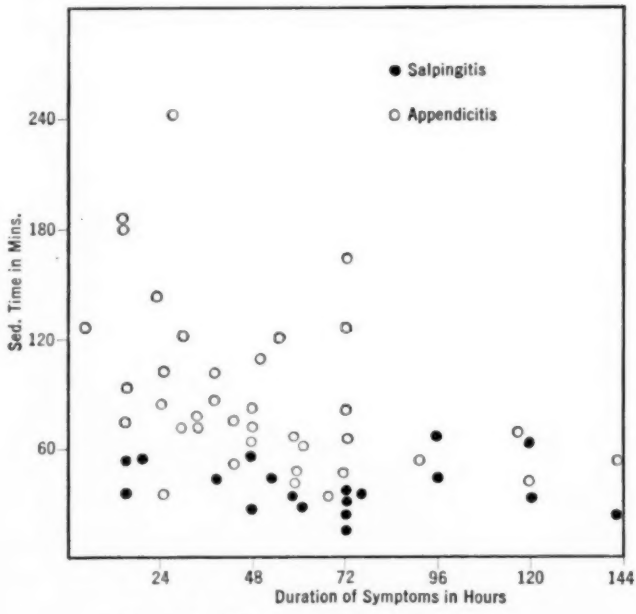

Chart I.—Duration of symptoms in hours.

In a study of 19 cases of acute salpingitis and 38 cases of acute appendicitis, there is a definite suggestion that the sedimentation time may be of some value in differentiating these two conditions, *if the duration of symptoms when the test is made is taken into consideration.* During the first 24 or even 48 hours after the onset of *symptoms,* the sedimentation time is apt to be shorter in acute salpingitis than in acute appendicitis; an occurrence that is not

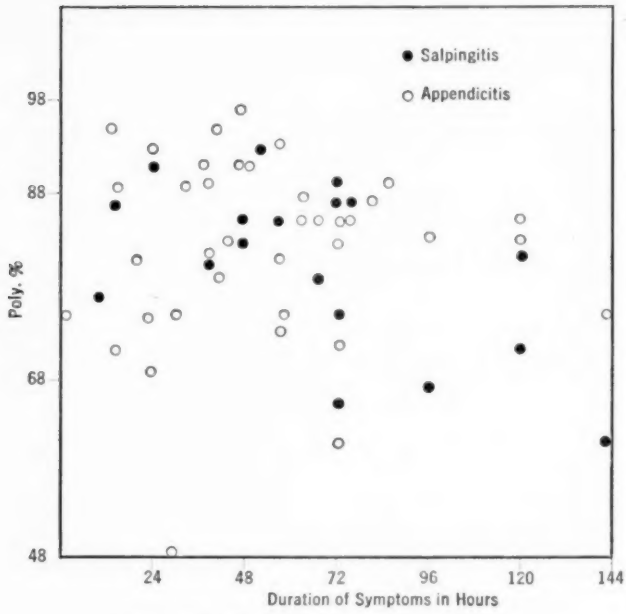

CHART II.—Duration of symptoms in hours.

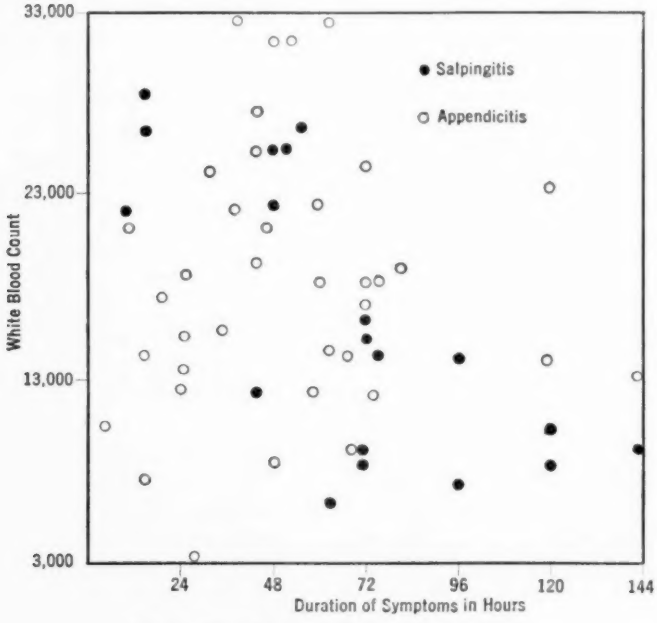

CHART III.—Duration of symptoms in hours.

unfailing, but frequent enough to be given consideration, as it is more uniform than either the leukocyte count or the differential.

These cases were not selected, except that care was taken to exclude other causes for alteration in the sedimentation time; such as pregnancy, tuberculosis, hemorrhage, anemia, the puerperal state, syphilis, and coincidental infection of other organs. For the estimation of the sedimentation time, the Linzenmeier method was used: 0.4 cc. of a 5% sodium citrate solution was drawn into a 2 cc. Record syringe. From a vein sufficient blood was drawn to make

TABLE 1.—APPENDICITIS.

No	Name.	Dur. of symptoms (in hrs.)	Sed. time (in mins.)	W. B. C. (thousand) (per c.mm)	R. B. C. (millions) (per c.mm)	Poly. per cent.	Operative findings.
1	F. R. Y.	2	126	10.2	...	75	Ac. appendicitis
2	J. R.	14	91	21.5	4.1	94	Ac. appendicitis
3	S. P. P.	15	186	17.5	5.0	88	Ac. appendicitis
4	R. C. F.	16	180	14.8	...	75	Ac. appendicitis
5	O. H. C.	16	71	7.6	...	71	Ac. appendicitis
6	M. E. B.	22	100	12.8	...	80	Ac. appendicitis
7	D. R. C.	24	150	16.8	...	68	Ac. appendicitis
8	W. A. C.	24	37	15.2	4.8	77	Ac. appendicitis
9	W. L.	24	88	13.9	...	74	Gang. appendicitis
10	C. J.	29	120	13.5	4.8	48	Ac. appendicitis
11	J. W.	30	240	24.0	...	92	Ac. appendicitis
12	S. T.	30	77	14.2	...	85	Gang. appendicitis
13	H. G. M.	32	70	15.6	4.0	75	Perf. appendicitis
14	S. M. M.	36	131	33.5	...	89	Gang. appendicitis
15	J. M. S.	36	70	22.2	...	89	Ac. appendicitis
16	D. R.	39	84	27.0	...	94	Perf. appendicitis
17	J. F. B.	42	103	21.0	...	81	Gang. appendicitis
18	R. O. G.	40	51	19.6	5.1	90	Ac. appendicitis
19	G. C. P.	45	75	25.5	...	83	Perf. appendicitis
20	A. M. C.	48	85	8.6	...	91	Ac. appendicitis
21	H. I. P.	48	63	31.3	4.2	90	Ac. appendicitis
22	E. L. C.	48	71	31.0	...	96	Perf. appendicitis
23	G. W.	55	41	12.0	3.8	81	Perf. appendicitis
24	B. A.	56	115	22.4	...	72	Gang. appendicitis
25	P. J. B.	58	110	51.3	...	93	Gang. appendicitis
26	R. E. L.	56	44	17.0	5.1	75	Perf. appendicitis
27	W. H. M.	60	64	14.2	...	87	Perf. appendicitis
28	A. S. F.	60	66	14.4	4.6	85	Perf. appendicitis
29	C. M.	72	48	18.0	...	85	Gang. appendicitis
30	D. L. J.	72	80	12.8	...	82	Perf. appendicitis
31	H. L.	72	33	24.8	4.5	85	Gang. appendicitis
32	E. R.	72	67	17.1	5.4	60	Ac. appendicitis
33	V. S.	72	163	9.2	4.7	71	Ac. appendicitis
34	P. M. W.	72	126	18.2	...	87	Gang. appendicitis
35	C. L. D.	88	58	19.4	...	88	Gang. appendicitis
36	D. P.	120	41	23.6	4.3	85	Perf. appendicitis
37	P. T.	120	67	14.0	...	84	Gang. appendicitis
38	W. W.	144	41	13.0	4.2	74	Perf. appendicitis
Average		50.2	70	18.9		81.5	

NOTE.—All these cases had negative Wassermann tests, and were negative for tuberculosis clinically.

2 cc. of the mixture. This was mixed then transferred to a 1 cc. serologic pipette graduated in 0.01. The time in minutes for the erythrocyte column to reach the 0.18 mark was recorded.

TABLE 2.—SALPINGITIS.

No	Name.	Dur. of symptoms (in hrs.).	Sed. time (in min.).	W. B. C. (thousands) (per c.mm.).	R. B. C. (millions) (per c.mm.).	Poly. per cent.
1	N. R. B.	14	56	22.4	4.8	77
2	L. E. J.	16	30	28.2	4.0	87
3	M. F. G.	22	58	28.6	5.1	91
4	M. M. P.	40	46	12.0	4.5	80
5	G. A. W.	48	28	22.8	4.0	83
6	N. L. A.	48	59	25.0	4.6	85
7	V. H. L.	52	42	26.9	4.4	92
8	M. E. T.	56	31	25.0	4.1	85
9	L. C.	60	30	6.2	4.4	77
10	M. P.	72	19	9.0	4.2	74
11	L. J. P.	72	28	17.2	4.3	89
12	I. McG.	72	34	8.2	4.8	65
13	E. G. B.	72	35	16.8	4.3	87
14	A. W.	76	45	14.6	4.9	87
15	E. W.	96	77	7.4	4.6	66
16	E. F. G.	96	46	15.4	4.0	83
17	S. B. G.	120	65	10.4	4.3	71
18	A. M. A.	120	38	8.4	4.9	81
19	W. W.	144	27	13.0	4.2	74
Average		68	41.7	16.7		80

NOTE.—All these cases showed acute salpingitis at operation, had negative Wassermann tests and were negative for tuberculosis clinically.

It will be observed in Chart I that in the cases of acute appendicitis, the sedimentation time is likely to be prolonged well over an hour within the first 48 hours after the onset of symptoms. After the 48 hours, there is a definite tendency for the sedimentation time to be shortened. On the other hand, in the cases of acute salpingitis, the time is not so prolonged, even in the 24-hour period from the onset of symptoms.

In accounting for this difference in the behavior of the sedimentation time in the two conditions, there can be no assumption that the difference in the infecting organism can be a factor. It may, however, be due to difference in the two organs as regards their function and nerve supply. The appendix is supplied by both sympathetic and parasympathetic nerve fibers. Gastro-intestinal symptoms occur for some time before there is any tenderness localized over the region of the appendix. Furthermore the appendix is a vestigial organ which is capable of only slight distensibility before it begins to cause symptoms. The Fallopian tube has only sympathetic nerve fibers;[2] it is a functioning organ which is capable of relatively great distensibility before causing symptoms. In Chart I it is shown that with the duration of the infection the sedimentation time becomes shortened in the case of acute appendicitis, and it may

be inferred that this is probably what happens in acute salpingitis. But in the case of salpingitis, the infection progresses further before giving symptoms. Therefore, the sedimentation time in acute salpingitis is shorter in the first 24 and 48 hours after onset of symptoms, because the infection had been there many hours before it began to cause symptoms.

Charts II and III are presented only to show that the leukocyte and differential counts are nothing like as uniform as the sedimentation time in differentiating the two diseases.

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ACUTE EOSINOPHILIC LEUKEMIA.

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The available literature contains reports of 3 instances of acute leukemia characterized by a preponderance of eosinophils in the peripheral blood and in tissue infiltrations.[1,2,3] The following case, with detailed postmortem observations is of interest because of the apparent rarity of the condition.

Case Report. D. K., a 17-year-old schoolgirl, was admitted to the Rochester Municipal Hospital on April 21, 1934. For the past 2 or 3 months small areas of discoloration of the skin had been noted from time to time. During this period her parents had noted gradually increasing pallor and limitation of exercise tolerance. For about 10 days there had been constant headache and for 7 days a purpuric eruption over the entire body. For 24 hours before admission there had been fever and prostration, with cyanosis and progressive dyspnea. The family history and the past history contributed nothing of importance.

At the time of examination, the rectal temperature was 39° C.; respiration 56 per minute. The patient was semi-comatose with marked cyanosis of the face, lips and nail beds. The skin of the face, trunk and extremities was covered with an ecchymotic and petechial eruption. Numerous petechiæ were scattered over the mucous membranes of the mouth and the conjunctivæ. A few small discrete nodes were felt on either side of the neck and in the right axilla, but there was no other glandular enlargement. Loud, moist râles were heard in both lungs. The heart was not enlarged to percussion; the sounds were very faint and of poor quality. The pulse was imperceptible and the blood pressure could not be obtained. The spleen and liver were not palpable. The tendon reflexes could not be obtained.

White blood cells numbered 130,000 per c.mm. The differential count was as follows: neutrophilic stab forms, 0.2%; segmented neutrophils, 9.8; eosinophilic stab forms, 1; segmented eosinophils, 67.6; neutrophilic

myelocytes, 2.6; myeloblasts, 16.6; lymphocytes, 2.2. The size and number of the granules in the eosinophils varied considerably; two and three lobed nuclei predominated. In counting 500 leukocytes, one nucleated red blood cell was encountered. There was almost complete absence of platelets in the smear. The blood Wassermann reaction was negative. It is unfortunate that there was no opportunity for more detailed laboratory studies. It was apparent from the appearance of the skin and mucous membranes that there was a moderately severe anemia.

The patient was admitted to the hospital at 2 A.M. and died 6 hours later.

AUTOPSY (Dr. Fischer, 2 hours after death). The body was that of a well developed and nourished white female. There were small petechiæ in the scleræ and conjunctivæ, the skin over the entire body, and at the tip of the tongue and in the mucous membranes of the mouth. The gums were pale and boggy.

Lymphatic System. There was no general glandular enlargement. A few discrete, shotty nodes were felt in both cervical triangles and there were several small glands in the right axilla. The abdominal lymph nodes and those at the hilum of each lung were small, pale and on section appeared quite cellular. There was one large gland at the hilus of the liver; on section this gland showed a grayish, cellular, surface with numerous small petechiæ. Retroperitoneal and pelvic glands did not appear grossly abnormal.

Heart. There were numerous small, subepicardial hemorrhages. The endocardium was dull, with numerous petechiæ. The myocardium was mottled, pinkish-yellow. On the cut surface, the inner two-thirds of the heart wall was yellowish-red, quite dull and opaque, as if extensively necrotic. At one commissure of the pulmonic valve there was a small, grayish vegetation, firmly attached to the vessel wall. There were several mural thrombi over the lower half of the inner surface of the left ventricle; many of these were firmly attached. The coronary arteries were patent throughout.

Lungs. The left weighed 800 gm, the right 600; both showed small subpleural hemorrhages with a mottled grayish-blue surface and felt subcrepitant throughout. The cut section was mottled, with many dark red areas. There was extreme congestion and edema.

The *spleen* weighed 150 gm. and was quite firm. The cut surface was grayish-pink, the Malpighian bodies poorly defined.

The *liver* weighed 1425 gm. The capsule was smooth and transparent. The cut surface was mottled, yellowish-brown in color. The portal areas were gray and opaque. No hemorrhages were seen in liver or spleen.

The *kidneys* each weighed 115 gm. and were similar in appearance. The capsule stripped easily, leaving a smooth surface with numerous petechial hemorrhages. The cut surface was pale. The mucosa of the kidney pelvis and of the ureters showed many petechiæ.

Gastro-intestinal Tract. There were many small petechiæ in the mucosa of the stomach and intestine and on the serosa of the small and large intestine. The solitary follicles and Peyer's patches were not more conspicuous than normal.

Pelvic Organs. The bladder mucosa showed many petechial hemorrhages. The uterus contained a small blood clot. No thrombi were found in the pelvic vessels.

Bone Marrow. Marrow from the middle third of the femur was grayish-pink in color and appeared quite cellular, as did the sternal, vertebral and rib marrow.

The *brain* weighed 1300 gm. The meninges were thin and transparent. Small petechial hemorrhages were seen both on the surface and cut surfaces. In some regions there were small areas which appeared somewhat softer than the surrounding tissue.

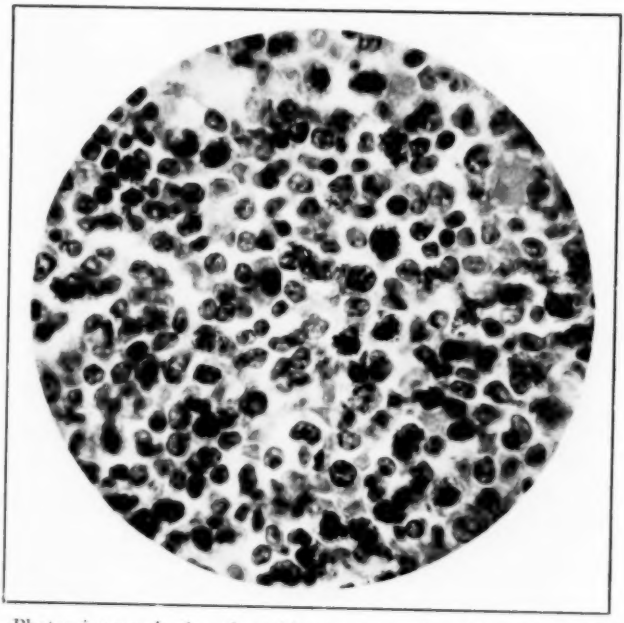

FIG. 1.—Photomicrograph of section of bone marrow from the middle third of the femur. (× 970).

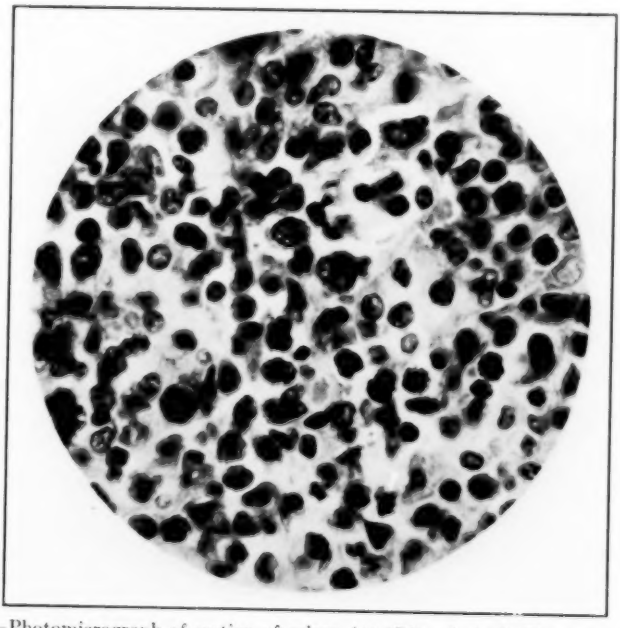

FIG. 2.—Photomicrograph of section of spleen (× 970). In both Fig. 1 and Fig. 2 the cells with granular cytoplasm are eosinophils.

MICROSCOPIC NOTES. *Heart.* In the subepicardial fat a few eosinophilic polymorphonuclear cells were seen. The inner half of the ventricular wall showed extreme inflammatory changes. There was partial or complete necrosis of much of the muscle. The necrotic areas were densely infiltrated with cells, most of which were eosinophils. An occasional eosinophilic myelocyte, neutrophilic myelocyte and very rare adult neutrophil could be identified. Many bacteria were seen in the necrotic areas and many of the small vessels contained infected thrombi. There was no evidence of healing. The endocardium was greatly thickened, infiltrated with cells and covered by antemortem blood clot. The outer half of the ventricle showed cloudy swelling only.

Lungs. There were small hemorrhages beneath the pleura and marked edema and congestion. Many alveoli were filled with well preserved red blood cells and only a few white blood cells. In some areas the alveoli contained an intensely cellular exudate consisting chiefly of eosinophils. Occasional eosinophilic and neutrophilic myelocytes were seen, with very rare adult neutrophils. There was very little peribronchial infiltration.

Spleen. The pulp was densely infiltrated with cells, many of which were eosinophils. Rare myelocytes and neutrophilic polymorphonuclears were scattered in small numbers among the numerous eosinophils and mononuclears. In some areas the infiltration was so dense that there appeared to be necrosis of the splenic pulp. The majority of the mononuclears were similar to those predominating in the bone marrow and occurring in large numbers in the lymph glands and portal spaces of the liver. These cells were obviously early cells, relatively undifferentiated in the hematoxylin and eosin sections. The nuclei were pale and occupied nearly all of the cell area; the cytoplasm was scanty and without granulations. Rare megakaryocytes were seen. The Malpighian bodies were small.

Liver. There was a moderate cloudy swelling with a few small areas of hemorrhage. Scattered eosinophils were seen in the sinusoids. The portal spaces showed a moderate infiltration with eosinophils and small, round mononuclears.

Kidneys. Occasional isolated hyalinized glomeruli were seen. There were a few small areas of hemorrhage. Between the tubules there were small collections of cells, for the most part eosinophils and small round cells with pale nuclei and very little cytoplasm.

Uterus. The musculature appeared normal but scattered eosinophils were seen between the muscle bundles.

Lymphatic System. The lymph nodes were very cellular but the normal structure could still be made out. The sinusoids contained many eosinophils and rare neutrophilic myelocytes and polymorphonuclears. There were large numbers of small, pale mononuclears similar to those seen in the spleen, kidneys and portal spaces of the liver. Several of the glands showed areas of hemorrhage. Occasional megakaryocytes were seen in the sinusoids. A few isolated nucleated red blood cells were identified. There was no evidence of fibrosis.

Bone Marrow. At the time of autopsy, 2 hours after death, a sample of sternal bone marrow was obtained and emulsified in the patient's serum. The cellular suspension was studied in supravital preparations stained with neutral red and Janus green and in fixed films stained with Wright's stain. Differential count of 1000 cells in the fixed preparation was as follows: neutrophilic myelocytes, 0.2%; eosinophilic myelocytes, 0.9; eosinophils with single lobe nucleus, 0.1; eosinophils with two lobed nucleus, 0.2; blast cells, 98.6. The blast cells presented pale nuclei, which in many instances contained nucleoli; the cytoplasm was moderately to deeply basophilic, without specific granules. No adult neutrophilic cells were seen. Very

rare megaloblasts, erythroblasts and normoblasts were seen but none were encountered in the differential enumeration of 1000 cells. No megakaryocytes were seen in either the fixed or supravital preparations. With the supravital stains the predominant cell was a rather small, mononuclear cell, the cytoplasm of which contained many mitochondria; a few of these cells contained one or two fine neutral red granules. It was thought that the majority of these cells were myeloblasts or "A" myelocytes (Sabin).

Sections from the marrow of the middle third of the femur, rib, vertebra, and sternum (hematoxylin and eosin and Giemsa) appeared very cellular, with the marrow spaces packed with small mononuclear cells similar to those described in the spleen, lymph glands, kidneys and portal spaces of the liver. Immature eosinophils were very conspicuous and numerous. In some areas eosinophilic myelocytes were so abundant that they completely dominated the picture. In other areas they were less prominent but always present in large numbers. Only occasional neutrophilic myelocytes and nucleated red blood cells were found. A few scattered megakaryocytes were seen.

Brain. The meninges were somewhat thickened and infiltrated with cells, many of which were eosinophils. Many of the small vessels in the meninges and in the brain substance contained thrombi. Small areas of hemorrhage into the brain substance were seen and there were several small areas of encephalomalacia.

Anatomical Diagnosis. Acute leukemia, with infiltration of bone marrow, spleen, lymph glands, liver and kidneys. Bronchopneumonia. Acute myocarditis with necrosis. Mural endocarditis. Thrombi in small radicals of cerebral vessels with focal areas of hemorrhage and encephalomalacia. Hemorrhages into skin, mucous membranes and viscera.

The clinical and pathologic observations establish the diagnosis of leukemia. The short duration of the illness, the presence of numerous very immature cells in the peripheral blood and tissue infiltrations, the terminal purpura and necrotizing infections are characteristic of the acute form of the disease. In view of the great predominance of eosinophils in the blood and tissues, the term "acute eosinophilic leukemia" is useful in differentiating this from other types of myelogenous leukemia. There was no clinical or pathologic evidence of trichiniasis, Hodgkin's disease or other condition which might have contributed to the striking eosinophilia.

Discussion. Previously recorded cases of acute eosinophilic leukemia conform to the above description of the disease except for minor details. (Schmidt-Weyland[1], Hay and Evans[2] and McCowan and Parker[3]).

Our case differs from these 3 chiefly in the longer duration, the presence of many myeloblasts in the peripheral blood, in the severity of the hemorrhagic phenomena and in the occurrence of terminal, agranulocytic inflammatory changes.

Acute leukemia is usually characterized by the extreme immaturity of the type cell in the peripheral blood and in the tissue infiltrations. In all 4 recorded instances of acute eosinophilic leukemia, however, the predominant cell in the peripheral circulation has been the adult eosinophil, with smaller numbers of cells of varying degrees of immaturity. Panton, in his discussion of the paper of

McCowan and Parker,[3] doubts the diagnosis of acute leukemia in such patients because of the predominance of mature forms in the peripheral blood. In spite of this unusual finding, the characteristic changes in the various organs have been those of undoubted leukemia in the 3 cases in which satisfactory autopsy material has been available for study. Hay and Evans observed that practically all of the eosinophils in the spleen and lymph nodes were mature forms, with very few eosinophilic myelocytes. They concluded that there was no histologic evidence of local production of eosinophils in any of the organs except the bone marrow. To investigate this point further, differential counts of the eosinophils were made by us in the fixed sections of various tissues of the patient here recorded. In appropriate sections, examined under the oil-immersion objective, the larger, non-lobulated, rather light staining nucleus of the myelocyte could be accurately differentiated from the smaller, lobulated, darker nucleus of the adult eosinophil. These differential counts (Table 1) show a proportion of myelocytes to adult eosinophils significantly higher in the bone marrow, spleen, lymph nodes and portal spaces of the liver than in other tissues. In these areas there were also large numbers of immature mononuclear cells with pale nuclei, similar to the predominant cells in the bone marrow thought to be very early myelocytes or myeloblasts on the basis of their supravital staining reactions. It seems reasonable to conclude from this evidence that the above mentioned areas were participating in the active production of eosinophils.

TABLE 1.

Tissue.	Eosinophilic myelocytes (per cent).	Adult eosinophils (per cent).
Bone marrow (femur)	96.5	3.5
Spleen	17.5	82.5
Abdominal lymph gland	28.5	71.5
Liver (portal spaces)	24.0	76.0
Liver (sinusoids)	7.0	93.0
Lung (bronchopneumonia)	3.5	96.5
Heart (necrotizing myocarditis)	4.5	95.5
Infected mural thrombus	5.5	94.5

It is of interest that the exudate in the areas of inflammation was composed almost entirely of adult eosinophils. Numerous lymphoid and other mononuclear cells were present but adult neutrophils were exceedingly rare. There was widespread necrosis and very little evidence of healing. The changes in the inflammatory areas suggested those seen in agranulocytosis except for the presence of large numbers of eosinophils. The striking lack of neutrophils in the peripheral blood and tissues is easily understood; neutrophilic myelocytes were extremely rare in the bone marrow and there was no evidence of any significant extramedullary neutrophilic myelopoiesis. These observations are in accord with those of Jaffe,[4] who has shown that the inflammatory defense response in

leukemia depends on the presence of myeloid tissue able to produce a sufficient number of mature neutrophils. Apparently the eosinophil is unable to assume the responsibilities of the neutrophil in the inflammatory defense reactions of the body.

Summary. A patient with acute eosinophilic leukemia is described. The clinical and pathologic features of the disease are similar to those observed in other types of acute leukemia, except for the type and maturity of the affected cell group. Evidence of extramedullary production of eosinophils is presented. Lack of adequate neutrophilic myelopoiesis was reflected in the scarcity of neutrophilic granulocytes in the necrotizing inflammatory exudates, which were composed chiefly of adult eosinophils.

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A QUANTITATIVE STUDY OF RENAL INJURY IN A CASE OF ACUTE POISONING BY BICHLORID OF MERCURY WITH A NOTE REGARDING TREATMENT.

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Numerous articles have appeared dealing with various aspects of acute mercury poisoning, both experimental and clinical. However, a careful study of the renal injury by means of recently improved kidney function tests, and as reflected by the quantitative study of abnormal aspects of the urine, is conspicuously lacking. It therefore seems timely to report such a study, made of a case of acute poisoning by mercuric chlorid, recently observed in our University Hospital.

Case Report. At about 4.30 A.M. on December 18, 1933, Mrs. B. V., aged 20, in an attempt to commit suicide swallowed half a glass of water into which were stirred "10 to 15 tablets" of mercuric chlorid. Each tablet contained 0.12 gm. of the salt. The total dose therefore was approximately 1.5 gm. About 10 minutes after ingestion of the poison, she vomited. Five minutes later she was caused to drink 3 pints of milk containing the whites of 5 eggs. Frequent emesis followed. She was admitted to the hospital 1½ hours after ingesting the poison, complaining of weakness, burning sensation in the mouth and pharynx, and epigastric pain.

On admission the patient was rational, oriented and coöperative. She

did not appear to be suffering. She was slightly pale. The pupils were equal, moderately dilated, and reacted normally to light and in accommodation. The ocular fundi were normal. The tongue and throat were red. Examination of the neck was negative. The lungs were clear. The heart was of normal size. Cardiac rhythm was regular. There were no murmurs. The pulse rate was 90. The blood pressure was 94/70. There was slight tenderness in the epigastrium and right upper quadrant of the abdomen. The extremities appeared normal. The tendon reflexes were normal.

The blood Kahn reaction was negative. The hemoglobin was 96% (Sahli). The red blood cell count was 5.33 million; leukocytes, 25,000 per c.mm., with 95% neutrophils. The red blood cells and platelets were normal.

On admission the patient's stomach was washed with a 5% solution of sodium bicarbonate. She was given 30 gm. of magnesium sulphate. The colon was irrigated. Several eggnogs were ingested during the first few hours in the hospital. Because the patient was unable to retain ingested food and fluids, the administration of intravenous fluids was begun on the morning of admission. On the first, second and third days, when vomiting was most profuse, both physiologic sodium chlorid, and 5% glucose solutions were given. Subsequently, 5% glucose alone was used. An average of 5000 cc. of fluid were given intravenously daily for 22 days. Each of the first 4 days the patient received 1 gm. of sodium thiosulphate and 3 gm. of sodium bicarbonate intravenously. Bowel movements were initiated by means of a tap water enema daily for 15 days.

The patient became progressively more ill during the first 5 days. Weakness was marked. Nausea and vomiting were particularly troublesome. During the first 5 days the vomitus was bloody. Diarrhea did not occur. On the fourth day, slight uterine bleeding began. (She had an abortion 10 weeks prior to admission, and since that time had had irregular uterine bleeding.)

On the fifth day the patient was very ill. Throughout most of the day she was semicomatose. On the following day the patient became oriented and fully conscious; however, she remained critically ill. Anorexia, nausea, gastric distress and vomiting continued to be the predominant features of her illness. Attempts to eat and drink were followed by vomiting.

Her condition did not change essentially until the 14th day when she complained less of nausea, and seemed brighter and more responsive. From this time on there was progressive improvement. About the 17th day she began retaining sips of water and small amounts of liquid nourishment. Her ability to retain ingested food and fluid gradually increased, but not sufficiently to permit the stopping of intravenous fluid until the 23d day. She was then given abundant fluids orally, and a soft diet containing about 50 gm. of protein daily. Improvement continued and the patient was discharged from the hospital on January 15, 1934. She was advised to continue restriction of activity, copious intake of fluid and the soft diet with restricted protein.

Frequent visits as an out-patient allowed us to follow her subsequent course, until we considered complete cure had resulted, 3½ months after the poisoning.

Renal Studies. Throughout the illness quantitative studies of the kidney injury were made. Renal function was measured by the urea clearance method of Van Slyke,[1] by concentration test according to the improved technique of Lashmet and Newburgh,[2] and by phenolsulphonephthalein excretion. Proteinuria was measured

by the Lashmet-Newburgh method.[3] Formed elements in the urine were counted after the manner described by Addis.[4] Frequent determinations of the non-protein nitrogen in the blood were made.

The urinary abnormalities and blood findings appear in Table 1. The results of the renal function studies, together with some of the other more important data, are presented graphically in Fig. 1.

TABLE 1.—URINE AND BLOOD FINDINGS.

	Urine findings.							Blood findings.				
				Formed elements excreted per 12 hours.*								
Date.	Volume, cc.	Reaction to litmus.	Protein, gm. per 24 hrs.	Casts.	Renal epithelial cells.	Leukocytes.	Erythrocytes.	Hemoglobin, %.	Red blood cells, millions per c.mm.	White blood cells, per c.mm.	Non-protein nitrogen, mg. %.	Carbon-dioxid combining power, vol. %
Dec. 18	1700	Acid	8.5	Many hyalin and granular	90,000,000	Few	Few	96	5.33	25,000		
19	2400	Acid	22.0	185,000 hyal. and gr.	144,000,000	Few	2,232,000†	..	....	...	45.1	
20	4400	Alk.	12.0	....	489,000,000	Few	3,720,000					
21	3900	Alk.	3.7	....	318,000,000	1,344,000	17,550,000‡	..	....	...	46.9	
22	4800	Neut.	2.45	298,900 hyalin	51,319,000	1,344,000	895,000	..	....	12,200	39.7	45.1
23	3800	Neut.	....	672,000	27,580,000	1,515,960	2,122,344					
24	3630	..	1.24									
25	3600	..	0.72									
26	2180	..	0.56	....	....	...	...	..	....	...	53.1	
27	5090	..	....	....	....	...	...	88	5.8	11,200		
28	3280	..	0.57									
29	4850	..	0.66	....	....	...	...	..	....	...	57.0	
30	5050	..	0.55									
31	3150	..	0.99									
Jan. 1	4000											
2	5580	..	0.60									
3	3700	Acid	....	230,000	1,500,000	Few	2,500,000					
4	4570	..	....	....	....	...	...	..	....	...	32.9	
5	4000	..	2.5‡	....	....	...	Grossblood‡	..	....	...	32.6	
6	3460											
7	3420											
8	4700	..	1.7‡									
9	2250	..	0.42									
10	2300	..	0.36									
11	1550											
12	1700	..	0.40	....	....	...	...	67				
13	2020	..	0.30	....	....	...	...	69				
14	2700	..	Trace									
27	..	Acid	Faint trace	35,064 hyal. and gr.	657,000	11,000,000	2,235,000					
Feb. 7	..	Acid	0	0	0	Few	0					
28	..	Acid	0	0	0	Few	0					
Apr. 5	..	Acid	0	0	0	8,605,000	210,000	85	4.8	8,900		

* At times urine collected for urea clearance tests was used for counting formed elements in the sediment. These counts were converted to values per 12 hours.
† Urine obtained by catheter.
‡ Uterine bleeding occurred on these days.

Gross urinary abnormalities existed during the first few days. Proteinuria was great during the first 3 days, the maximum amount of protein (22 gm.) being excreted on the second day. It gradually diminished after the third day, although it persisted for more than 6 weeks. Sporadic increases are noted at times when uterine bleeding occurred.

Cylindruria was also great during the first few days. The maximum was recorded on the sixth day. When the urine was alkalin cast counts were not attempted. Casts were found as long as there was proteinuria.

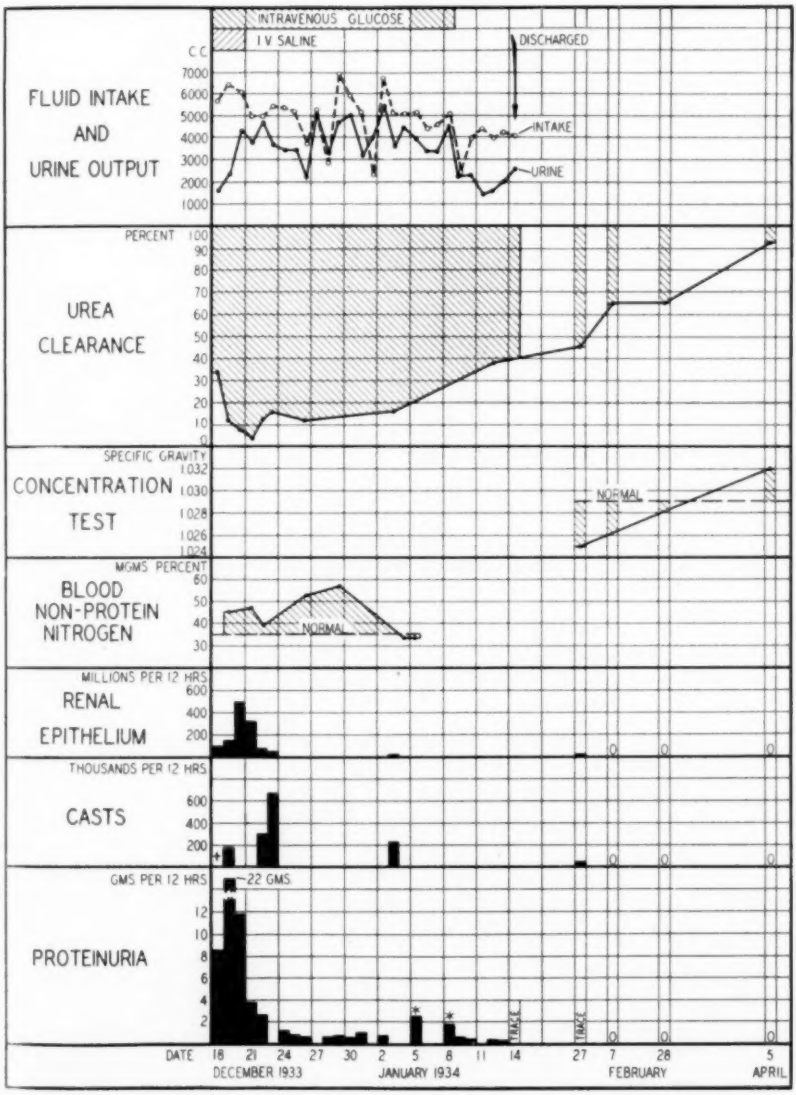

FIG. 1.

* Bloody urine (uterine bleeding).

The most remarkable abnormal finding in the urine was the excretion of huge numbers of renal epithelial cells during the first few days. These cells were excreted in increasing numbers until the third day, when the maximum of 489,000,000 were found in a 12-hour period. There was a rapid decrease in the excretion of renal epithelium after the third day, although these cells were seen in small numbers as long as proteinuria was observed.

The number of leukocytes seen in the urine was never strikingly abnormal.

Evaluation of the erythrocytes observed in the urine is difficult due to the fact that uterine bleeding occurred at times. However, the urine obtained by catheter on the second day contained slightly more red blood cells than was observed in normal individuals by Addis.[5]

The renal function studies, and especially the results of the frequent urea clearance tests, are most instructive.* The urea clearance test shown on the graph for the first day was done 6 hours after the patient was admitted (7½ hours after taking the poison). This early kidney function was only 34% of normal. The function continued to fall until it reached the low value of 5% of normal on the fourth day, after which it remained between 10% and 17% for 2 weeks. Throughout this time the blood non-protein nitrogen rose only slightly, the highest value (on the twelfth day) being 57 mg. per 100 cc. of blood. There was a gradual increase in the urea clearance during the third and fourth week, but by the time the patient was discharged from the hospital it had risen to only 39% of normal.

On the patient's first return visit, January 27, she felt much improved. Urea clearance was 46% of normal. On this date a concentration test was done. It showed impairment of renal func-

* In doing the urea clearance tests, the method used to determine the urea content of blood and urine requires the digestion of urea by the enzyme urease. It is known that mercury, if present in a sufficient quantity, interferes with the activity of urease. Since mercury is excreted in the urine of patients poisoned with bichlorid of mercury, it was necessary to determine whether the sample of urine used in performing these tests contained enough mercury to interfere with the urease digestion. Accordingly, urease digestions were carried out on standard solutions of urea, to which different amounts of mercuric chlorid were added.

Following are the results:

Added $HgCl_2$, mg.	Added mercury, mg.	Digestion, %.
0.02	0.0148	100
0.03	0.0222	96
0.04	0.0295	87
0.06	0.0443	81
0.10	0.0739	50

These findings show that there is no appreciable interference with urease activity unless 0.03 mg. of mercury is present. Considering the large volume of urine excreted by this patient each day, it is unreasonable to believe that the concentration of mercury in the urine was sufficiently great to interfere with the activity of urease.

tion. The maximum specific gravity was 1.025. Normally, by the technique used, it is 1.029 or above. Excretion of 6 mg. of intravenously injected phenolsulphonephthalein was as follows: 30 minutes after injection, 40% return of dye; 60 minutes, 10%; 120 minutes, 10%; a total of 60%. On February 7, for the first time, the urine showed no abnormality. The urea clearance, however, remained below normal, being only 66%. On February 28, the same urea clearance value was observed. On this day the patient complained that her hands felt swollen. No edema was observed. Blood serum showed the following protein content: Total protein, 7.2 gm. per 100 cc.; albumin, 4.75 gm.; globulin, 2.45 gm. The albumin/globulin ratio was 1.9.

The patient was not seen again until April 5, 1934. On this date she returned feeling entirely well. She had gained 5 pounds in weight. Increasing activity had been attended by no symptoms. Physical examination was negative. Urinalysis showed no abnormality. Urea clearance was 92%. Concentration test showed normal ability to concentrate the urine, the maximum specific gravity being 1.032. Excretion of 6 mg. of intravenously injected phenolsulphonephthalein was also normal: 30 minutes after injection, 50% return of dye; 60 minutes, 15%; 120 minutes, 10%; a total of 75%. Since there was no evidence of renal damage, the patient was considered completely cured.

Discussion. The most interesting aspect of this case is the course of the renal changes. Within a few hours after ingestion of the nephrotoxic substance, marked renal damage existed as shown by gross proteinuria, cylindruria, the excretion of large numbers of renal epithelial cells, and serious impairment of kidney function. Seven and a half hours after the poisoning the urea clearance was only 34% of normal, and the very low level of 5% of normal was reached on the fourth day. The renal function remained at a strikingly low level for 2 weeks, after which continued improvement occurred. In contrast to the rapid decrease, improvement of kidney function was relatively slow, and normal function was not noted until 3½ months after the poisoning.

It should be noted that impairment of function existed several weeks after the urine ceased to show any abnormality. On each occasion when simultaneous renal function tests were done, there was good agreement between the results of the concentration test and the urea clearance test.

Of particular interest is the fact that during the time when there was marked kidney damage as shown by the low urea clearance values, and throughout which time vomiting was profuse, the nonprotein nitrogenous wastes in the blood were never found to be higher than 57 mg. %. This we feel is due to a provision for a

high fluid intake *from the outset*, thus allowing sufficient solvent for excretion of the waste products.

At this point a brief consideration of the treatment of acute mercurial poisoning is *apropos*. Therapy for this type of poisoning can be divided into four main headings: (1) measures to prevent absorption and rid the patient of the unabsorbed poison; (2) treatment of shock, if it occurs; (3) measures to detoxify the absorbed mercury; and (4) measures to correct, or compensate for, functional disturbances resulting from the poison.

There can be no doubt about the importance of preventing the absorption of the poison, and of causing its rapid evacuation. The methods to be used are too well known to warrant further comment here. The suggestion made by Mintz[6] that, as a prophylactic measure, tablets of mercury bichlorid be coated with an emetic such as copper sulphate, seems wise.

Antishock treatment is amply discussed elsewhere, and will not be dealt with in this paper.

McBride and Dennie[7,8] have advised the intravenous use of sodium thiosulphate, claiming that detoxication resulted in the body. However, the animal experiments of Haskell, Henderson and Hamilton,[9] Melville and Bruger,[10] Young and Taylor[11] and others, show unquestionably that this medication is of no clinical value. To date no successful antidote for absorbed mercury has been demonstrated.

Measures to be taken to combat the abnormal physiology resulting from damage caused by the poison, deserve more consideration. The pathology of greatest clinical importance is, in most cases, the kidney damage. That this is rapid in development and causes marked impairment of the function of these organs is well illustrated by this case.

It has been demonstrated by one of us (F. H. L.)[12] that the damaged kidney needs much more fluid with which to excrete waste products. The amount needed depends upon the extent of the kidney damage. If sufficient fluid is provided, *even in the presence of marked renal damage*, there is satisfactory excretion of wastes, and retention does not occur.

The choice of fluid to be administered is important. In most cases of mercury bichlorid poisoning, profuse vomiting occurs. In this way much of the body chlorid may be lost. Peters, Eisenman and Kydd[13] have recently shown that the circulating chlorids are diminished in most cases of acute mercurial poisoning. They advise the administration of a large volume of a physiologic solution of sodium chlorid in order to restore normal concentration of chlorid in the body fluids.

Excessive amounts of sodium salts, however, we feel should not be given since storage of sodium will increase the tendency to edema that is prone to occur in cases of severe poisoning with mercury.

Reason for guarding against edema lies in the fact that the kidneys will share in any generalized edema, and edema of the kidneys would further impair the function of these organs. Consequently, when it is desirable to administer abundant fluid intravenously, we believe physiologic saline solution should be used only when a definite need of chlorid exists. In all other circumstances we prefer to use a 5% solution of glucose. The glucose is burned, furnishing a small supply of energy, and preventing the occurrence of ketosis.

That 5% glucose can be administered intravenously in large amounts daily for a long time with no harmful results is shown by this case. On each of the first 3 days, when vomiting was most profuse, 2 liters of physiologic saline were given intravenously, followed by 3 liters of a 5% solution of glucose. After the third day, 5% glucose alone was administered. An average of 5000 cc. were given daily through the twenty-second day. Thus an average output of over 3700 cc. of urine occurred daily. It is to be noted that in the presence of marked renal damage there was no difficulty in eliminating this large volume of urine and that edema at no time was present.

Conclusions. 1. A quantitative study of the renal injury in a case of acute poisoning with bichlorid of mercury is reported.

2. It is shown that extensive renal damage accounting for marked impairment of function occurred almost immediately, and existed for several weeks, after which there was progressive but relatively slow improvement until normal function returned 3½ months after the poisoning. Impairment of renal function continued for weeks after all urinary abnormalities had disappeared.

3. The treatment of acute mercury poisoning is briefly discussed. The importance of the administration of a large amount of fluids *from the very outset*, to compensate for the impairment of renal function, is pointed out. Indications for the use of physiologic solutions of saline and of glucose are discussed.

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ACUTE POTASSIUM BICHROMATE POISONING.

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Chronic chromium poisoning is met with not infrequently in industry, but acute potassium bichromate poisoning from a single large dose taken by mouth is relatively uncommon, 69 cases having been reported. Reischer and Glesinger[1] in reporting a case made a comprehensive survey of 63 cases which they found in the literature. They overlooked a case reported by Philipson.[2] Jonsson,[3] Bernard,[4] and Biancalani[5] have reported 4 cases since 1922.

Table 1.—Urinary Findings.

	Urine.	Alb.	Urinary findings.			
			Sp. gr.	N. P. N. mg.	Creatinin in 100 cc.	Icteric index.
Feb.						
25	Acetone	++				
27	Acetone	+				
Mar.						
1	Oliguria Few R. B. C. and W. B. C.	+	1012	150	6.75	
2	Oliguria Few R. B. C. and W. B. C.	+	1010			
3	Oliguria Few R. B. C. and W. B. C.	+	1010			9
4	Oliguria Few hyalin and granular casts Few R. B. C.	+++	1012	205	8	
6	Oliguria Few R. B. C.	++	1010	200	7.5	
8	Sediment—neg. Urine output normal	+	1012	150	5	
10	Few W. B. C. (uncatheterized specimen)	++	1010	90	3.75	
13	Same			47.5	1.9	9
15	Same			43	1.5	
17	Same			30	1.3	
22	Same			26	1.2	8
29	Same			26	1.15	
June						
28	Amber—cloudy Acid Micro, few R. B. C. Loaded c. epith. cells and bacteria	ft. tr. Feels fine,	1018 gained	27 30 lbs.)	Cholesterol 174 Cholesterol 84 esters B. P. 140/100	

The following case, the first to appear in the literature of this country, is illustrative of those previously described.

Case Report. Patient I. O., aged 25, was admitted to the hospital on February 25, 1933, complaining of dizziness, intense thirst, vague abdominal pains, and vomiting of greenish-yellow fluid which was sometimes blood streaked. Her illness began on February 23, with a paroxysm of vomiting. No other symptoms were elicited. The family and past histories were unimportant.

FIG. 1.—Toxic rash.

Physical examination revealed a thin, white female, not acutely ill. The skin was dry and inelastic. There were no other positive findings. The rectal temperature was 100°, pulse 90, respirations 24, and blood pressure 90/60. The urine showed only 2+acetone. The patient was neurotic, very uncoöperative, and refused the routine blood chemistry.

Two days after admission, she complained of a dull pain in the epigastrium and right upper quadrant, which were tender and rigid. The next day, the temperature rose to 101°, the pain, tenderness and rigidity became more severe and the liver edge was felt 1 inch below the costal margin. There was no jaundice, but she continued to vomit once or twice a day.

During the next 4 days, the signs and symptoms referable to the liver disappeared and the temperature became normal.

Four days after admission, she became more coöperative, and the following laboratory reports were obtained. The blood Wassermann and Kahn tests were negative, the blood count showed 15,000 leukocytes with 87% polymorphonuclear leukocytes and 13% lymphocytes; the red blood cell count was 4,300,000 and the hemoglobin 85% (Sahli); the blood non-protein was 150 and the blood creatinin 6.75 mg. 100 cc. The 24-hour urine output was 600 cc.; the specific gravity was 1.012, there was a trace of albumin, a few R. B. C. and W. B. C. With these findings of severe nephritis preceded by severe hepatitis, the patient was closely questioned but denied having taken any medication before admission. A urine analysis was negative for mercury.

On March 4, the blood non-protein nitrogen had risen to 205 and the creatinin to 8. There was still an oliguria and the urinary findings continued to indicate renal damage. The feces contained occult blood. At this time, the patient did not seem very ill except for the marked dehydration which persisted in spite of a large fluid intake. On this day, an erythematous, pin-point, macular rash appeared on the arms and legs. It faded on pressure, and did not itch. It spread rapidly and became confluent. The attending dermatologist diagnosed it as a non-specific toxic rash. It began to fade on March 8 and disappeared on March 13.

On March 5, the patient admitted that on February 23d, she had swallowed a heaping teaspoonful of orange-yellow crystals dissolved in water. The original bottle was obtained, and found to contain potassium bichromate crystals. The urine, repeatedly analyzed for chromium, was reported positive by Dr. P. A. Riedal, the hospital pathological chemist. This was verified by Dr. A. C. Gettler, the New York City toxicologist.

The blood non-protein nitrogen and creatinin reached normal on March 17. After the initial oliguria, the urine volume rose rapidly to normal, but the specific gravity remained low throughout, and there remained a trace of albumin and a few W. B. C. in uncatheterized specimens. The vomiting ceased on March 12. Fishberg concentration tests were done frequently and showed a low fixed specific gravity ranging between 1.008 and 1.012; an isolated reading of 1.022 was obtained near the end of her hospital stay. Two urea clearance tests (March 22–29) showed 80% of normal function. The serum albumin was 2.6% and the serum globulin was 1.3% on March 6. The cholesterol was 160 on March 22. The blood pressure remained low throughout, averaging about 100/70. The temperature, pulse rate, and respiratory rate remained normal except for a temperature of 101° on February 28. Roentgenograms of the heart, lungs, and abdomen were normal. A blood count (March 28) showed 8100 leukocytes, 81% polymorphonuclear leukocytes and 19% lymphocytes; the red blood cell count was 3,900,000 and the hemoglobin 70% (Sahli).

The patient was discharged on April 2, in good health. She was seen again on June 28. She was enjoying excellent health and had gained 30 pounds. Her blood pressure was 140/100; her N. P. N. was 27; her urine showed a specific gravity of 1.018, and was essentially normal.

The treatment was entirely symptomatic. Fluids were administered by mouth, hypodermoclysis and proctolysis. High hot colonic irrigations were given when the diagnosis was made.

Summary. 1. A case of acute potassium bichromate poisoning with recovery is reported. There are no other reports in the literature of the United States.

2. The features of this case are the presence of an enlarged tender

liver, a skin eruption and the finding of chromium in the urine. Previous case reports fail to mention such findings.

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THE CLINICAL APPLICATION OF DUODENAL EXTRACT (MACALLUM–LAUGHTON) IN DIABETES MELLITUS.

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The possibility that an agent is produced in the duodenal mucosa when food is ingested, which activates the internal secretion of the pancreas, as secretin liberates the external secretion, was considered, in 1906, by Moore *et al.*[1] These investigators claimed benefit from secretin—perhaps unpurified—in the treatment of 3 diabetics but their findings were not confirmed. In 1 of the cases the results seemed conclusive.

Ivy and Fisher,[2] in 1924, isolated an insulin-like substance from the mucosa of the stomach and duodenum, and Dixon and Wadia,[3] in 1926, obtained an insulin-like action with duodenal extracts given to dogs subcutaneously.

Macallum,[4] in 1929, stated that, in his belief, there was an insular hormone produced in the duodenum when sugar entered the intestine. Heller,[5] in 1929, found a lower induced hyperglycemia after giving an extract of the duodenal mucosa to rabbits and dogs than when none was administered.

In 1930, Laughton and Macallum[6] reported that a duodenal extract, prepared by them, influenced the curve of an induced hyperglycemia in the normal but not in the depancreatized animal.

Laughton *et al.*,[7] in 1931, stated that clinical results appeared to parallel those obtained on animals. The beneficial effects were confined to the mild diabetic not requiring insulin. There were no case reports.

In 1932, Laughton and Macallum[8] reported, in detail, the effect of a duodenal extract on dogs and rabbits. This preparation is the one used in the present clinical study. The extract, obtained by acid extraction from beef mucosa, had no effect on the normal blood sugar of rabbits, but it moderated the hyperglycemia artificially induced by giving glucose intravenously and when epinephrin was given. This effect lasted, after a period of 7 to 10 days' administration, for about 2 weeks. There was no effect on the normal blood sugar or in the totally depancreatized dog, but the partially depancreatized dog was benefited by subcutaneous and oral administration of the extract. It was proved that the extract did not contain secretin or insulin.

La Barre,[9] in 1932, obtained by acid and alcoholic extractions from the duodenal mucosa a substance which he called incretin. Given intravenously, orally or subcutaneously to rabbits and dogs, it produced hypoglycemic convulsions and in some instances death. Unlike the Macallum-Laughton preparation, incretin lowered the blood sugar of the normal dog but it too had no effect on the blood sugar of totally depancreatized animals.

In the fall of 1932, our study with the Macallum-Laughton extract on human diabetics was begun.

The behavior of the blood sugar and its responses to diet and insulin are so variable in the diabetic that conservatism must attend any conclusions. We must remember that improvement may ensue with changes in diet alone. This factor has undoubtedly influenced our results, though we believe we have in all fairness planned this study in such a way as to assess fairly the activity of the remedy employed.

Methods. Increases in carbohydrate and total calories to the limit of tolerance before, and further increases after beginning the extract have been made to observe changes in tolerance.

In mild diabetics, with a relatively high tolerance for carbohydrate and total calories, glucose tolerance tests were employed. The curves obtained were used as a measure of improvement. In these tests 100 gm. of glucose were given in 250 cc. of water and blood and urine specimens were obtained before the glucose was given and at intervals of ½, 1, 2 and 3 hours after. These tests were made before, during and at varying intervals after extract treatment.

The free use of tolerance tests in this study must not be interpreted as a usual or common practice in the routine management of our diabetics. Aside from this investigation we avoid glucose tolerance tests in all diabetics except where no other test establishes the diagnosis. Furthermore, we have used the tests only when better methods of proof were not applicable.

The effect of the abrupt withdrawal of large doses of insulin before and after the use of duodenal extract has been observed and the approximate period of apparent effectiveness has been roughly estimated by observing

laboratory data over long periods. Subsequent increases in the carbohydrate and total calories were made to find the limit of tolerance.

The blood sugar estimations were done by the new Benedict method,[10] in the Jefferson and Pennsylvania Hospitals, until May 1, 1934, when the old Benedict method was resumed at the Pennsylvania Hospital.

The patients were hospitalized throughout the study except when otherwise specified.

While Macallum and Laughton have administered the extract subcutaneously to animals, we have given it by mouth only. At first we gave 1 gm. ½ hour before each meal, but as little effect was obtained in the first 2 or 3 days of treatment it seemed that administration in direct relationship to meals was unimportant. Larger doses, up to 6 gm. t. i. d., did not increase the effect. In fact 0.25 gm. given t. i. d. was suitable and we suspect that smaller doses are effective.

Short courses of treatment, 1 week in each month, were tried when the apparent effect was carried over from days to weeks after withdrawal of the extract.

Illustrative Cases. Case 1.—T. G. (Penn. Hosp. No. 17176), male, colored, aged 16, was admitted on July 9, 1934, complaining of increasing drowsiness, loss of appetite, strength and weight with an unquenchable thirst and polyuria of 4 weeks' duration.

Family History. One sister had glycosuria, otherwise unimportant. *Past illnesses* comprised of measles in childhood and he was thought to have a mild hypopituitarism (dystrophia adiposa genitalia) in 1930. At that time glycosuria, which cleared up promptly, was found.

Present Illness. Four weeks before admission he lost all desire for cigarettes and at the same time weakness, thirst, polyuria, dryness of the skin, constipation and anorexia became noticeable. These symptoms increased in severity until admission. In the month preceding his admission he lost in weight from 82 to 71 kg.

Physical Examination. Pronounced drowsiness, dry skin, nutrition good, intraocular tension normal to digital pressure and infected tonsils. The heart, lungs, abdomen, genitalia and reflexes were normal; the blood pressure was 120/80; height, 71½ in.

Laboratory Data. Heavy glycosuria with strong reactions for acetone and di-acetic acid in the urine. The blood sugar was 0.263%, with a severe grade of lipemia and a strong positive reaction for acetone and di-acetic acid in the blood plasma (Rothera-Wishart test). Additional data are included in Table 1.

Table 1.—Data in Study of Case 1.

Date, 1934.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.	Wt., kg.
	P.	F.	C.	Cal.					
7/ 9– 7/12	85	47	160	1400	44–104	None	263– 67	42.6–50.2	68
7/13– 7/22	85	55	140	1400	70–106	None	183–100	30.8– 4.2	71
7/23– 7/30	85	22	140	1100	100–109	None	103–131	3.4–11.9	75
7/31	85	22	140	1100	None	None	....	14.9	
8/1	85	22	140	1100	98	None	122	2.5	
8/2–8/6	85	22	140	1100	None	None	145–154	12.7–31.9	
8/7	85	22	140	1100	71	¼ gm. q.i.d.	183	7.0	
8/8–8/13	85	22	140	1100	106	"	142	5.3– 7.0	75
8/14–8/23	85	22	140	1100	None	"	138–119	1.0–9.1	
8/24	85	22	140	1100	110	"	126	5.8	
8/25–9/5	85	22	140	1100	110	None	126–160	2.2– 6.0	
9/6–10/5	85	22	140	1100	None	None	152–102	1.0– 9.7	75–72

He improved steadily. The insulin was increased daily until the blood sugar was normal. A gain in weight from 68 kg. on July 10 to 77 kg. on July 22 followed the alleviation of the ketosis.

Progress Notes. Prior to duodenal extract therapy his actual insulin requirement was 106 units daily, given in 4 doses. As will be seen in Table 1, with the blood sugar at 0.103% (July 30) when no insulin was given, a loss of 14.9 gm. of sugar in the urine resulted. On the following day, 98 units of insulin reduced the sugar loss to 2.5 gm. From August 2 to 6, when no insulin was given, the blood sugar steadily increased from 0.122% to 0.183% (August 7), with an average daily glycosuria of 24 gm.

With reduction of blood sugar by insulin, duodenal extract (No. 3041362) was begun in doses of 0.25 gm. q. i. d. on August 7. During 11 days (August 14 to 24) of duodenal extract without insulin an average daily loss of 6.3 gm. of sugar ensued, as compared with 24 gm. before the extract was given. The blood sugar increased but little (0.133% to 0.138%) and then fell to normal.

That this improvement might be due to an improved tolerance irrespective of the extract was considered possible. If this were so then the patient would not be expected to tolerate the former dosage of insulin without hypoglycemic reactions. A higher dosage, 110 units, was given, and no insulin reactions were subjectively or objectively noted. This dosage was continued for 13 days (August 24 to September 5, inclusive), the duodenal extract having been stopped on August 24.

There was an increase in the blood sugar to 0.152% on September 7, after stopping 110 units of insulin on September 5, but it decreased on September 10 to 0.120%, a lower value than obtained when 110 units of insulin were given. There was a slight increase in the sugar loss. After a transitory increase in the blood sugar (0.143% on September 14), normal values were restored (0.102 to 0.122%, September 9 to October 2).

We attribute this improvement, without insulin since September 5, to the duodenal extract administered between August 6 and 25.

Glycosuria, due to a proved low renal threshold, persisted throughout.

A glucose tolerance test on October 5 gave the following blood sugar values: Fasting, 0.113%; 1st hour, 0.177%; 2d, 0.117%; 3d, 0.118%. This test was repeated on November 6, the diet having been increased to protein, 85 gm., fat, 94 gm., carbohydrate, 150 gm. (1800 calories), on October 30, with the following results: Fasting, 0.128%; ½ hour, 0.166%; 1st hour, 0.147%; 2d, 0.110%; 3d, 0.086%.

Subsequent tolerance tests on November 13, 20 and 27 revealed curves reverting to the diabetic type, the last being: Fasting, 0.146%; ½ hour, 0.179%; 1st hour, 0.166%; 2d, 0.193%; 3d, 0.154%. The latter course to poorer curves may be due, in part, to a larger diet—protein, 85 gm., fat, 18 gm., carbohydrate, 400 gm. (2100 calories)—begun on November 8.

SUMMARY OF CASE. 1. There was an average loss of 24 gm. of sugar and the blood sugar increased from 0.103% to 0.183% when 106 units of insulin were stopped. With the extract, 7 days later, the same amount of insulin was discontinued. A daily average sugar loss of 6.3 gm. followed while the blood sugar increased from 0.133% to 0.138% only, and was followed by a drop to normal, 0.119%. That this was due to improvement in tolerance without any aid from the extract seems unlikely when the patient later tolerated a larger dose of insulin, 110 units daily, for a period of 13 days without insulin reactions.

2. It would appear that the extract continued to exert an effect

in this case for at least 73 days after it was stopped as a normal glucose tolerance curve was obtained, November 6. A progressive decrease in tolerance ensued after this date.

3. There is no evidence that the effect of the extract is added to that of the insulin, but rather that its effect is in abeyance while insulin is being given.

We consider the foregoing as unusual in a young diabetic who was in impending coma less than 3 months previously.

Case 2.—R. M. (Penn. Hosp. No. 31760), a colored male, aged 44, was admitted to Dr. McCrae's service in a semiconscious condition from diabetic ketosis on September 22, 1933. He had no knowledge of having diabetes until August, 1933, when weakness, anorexia, polyuria, thirst and loss of weight (18 kg. in 6 weeks) were observed. No infection had been present nor was any found on admission.

Past and Family History. Unimportant.

Physical Examination. Tissues dehydrated; skin dry; blood pressure, 100/60; tongue and pharynx dry; many carious teeth; soft systolic murmur at the cardiac apex; pulse rate, 120; moderate tenderness and rigidity in the epigastric region; height, 69 in.

Laboratory Data. The blood serological tests and, beyond a mild leukocytosis, the blood counts were normal. There were heavy reactions for sugar, acetone and di-acetic acid in the urine.

Progress Notes. The effect of stopping the insulin before and after giving duodenal extract was observed after his recovery from ketosis. On October 8 no insulin was given and on October 9 a small amount of sugar was lost in the urine. Insulin (32 units) was given on October 9 but was discontinued on October 10. A trace of sugar appeared in the urine on October 13, heavier reactions were found in 2 specimens on the 14th and in 3 on the 15th.

Duodenal extract (No. 3005889) was given, 1 gm. t. i. d. before meals, from October 14 to 23, inclusive. The glycosuria subsided at once.

A glucose tolerance test (October 30) gave the following blood sugar values: Fasting, 0.081%; 1st hour, 0.193%; 2d, 0.196%; 3d, 0.104%. The glycosuria amounted to 4.4 gm.

On November 6, 12 days without the extract, a better curve was obtained: 1st hour, 0.192%; 2d, 0.139%; 3d, 0.060%. There was a loss of 1.7 gm. of sugar in the urine.

The test was repeated on November 20, but through a misunderstanding 75 instead of 100 gm. of glucose were given. Allowing for this there was continued improvement. In fact, we regard the curve as normal. The blood sugar was 0.085% fasting, 0.150% the 1st hour, 0.080% the 2d hour and 0.049% the 3d hour. There was a trace of sugar in the urine. These results were obtained 27 days after the extract had been stopped.

In a test on November 12 (49 days without extract) the fasting blood sugar was 0.089%; the 1st hour, 0.180%; the 2d, 0.165%; the 3d, 0.090%. The test on December 26 (63 days without the extract) was: Fasting, 0.096%; 1st hour, 0.173%; 2d, 0.190%; 3d, 0.139%. Note the increase in blood sugar between the 1st and 2d hours. The glycosuria amounted to 3.7 gm.

Further reduction in tolerance was recorded on April 23, 1934. The peak was 0.224% the 2d hour; 0.144% the 3d hour. The glycosuria amounted to 3.2 gm.

On July 16 (266 days without extract) a still lower tolerance was shown by a curve having a peak of 0.297% at the 2d hour and a 3d-hour value of 0.223%. There was glycosuria (4.8 gm.). At no time was a hyperglycemia found between tolerance tests.

TABLE 2.—DATA IN STUDY OF CASE 2.

Date, 1933.	Diet				Duodenal extract.	Insulin, units.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
9/22– 9/27	70	110	140	1830	None	40–160	410–158	14 1 8 8
9/28–10/1	70	58	140	1360	None	120–84	207–66	Heavy to 0
10/ 2–10/7	70	91	135	1600	None	90–24	182	0
10/ 8–10/12	70	91	135	1600	None	32–0	. . .	0 to trace
10/13–10/23	70	91	135	1600	1 gm. t.i.d.	None	84–95	Mod. to 0
10/24, 1933, to 4/23, 1934	70	91	135	1600	None	None	60–118	0*

* Glycosuria occurred only after ingestion of glucose as noted in case report.

SUMMARY OF CASE. Improvement in the tolerance followed the use of the duodenal extract, greatest 27 days after the withdrawal of the extract. Four subsequent tolerance tests showed progressively poorer curves.

During the period of improvement the body weight increased from 67 to 71.8 kg. Further gain (71.8 to 78 kg.) ensued as the tolerance curves became less satisfactory. The increase in weight would tend to depress the tolerance and it might account for the poorer curves obtained on November 12 and December 26, but there was no increase after December 26 yet the tests became less satisfactory. We might expect the gain in weight from October 23 to November 20 to neutralize improving tolerance, but this was not evident.

CASE 3.—I. Z. (Penn. Hosp. No. 31768), male Hebrew, aged 65, was admitted on September 23, 1933, complaining of coldness of the extremities and slight swelling about the ankles.

Present Illness. The onset of symptoms, polyuria, polyphagia and pruritus, was in 1931. He received no treatment until February, 1933, when he came to the Out-Patient Metabolic Clinic. Examination revealed marked decrease in circulation in the legs and feet due to organic arterial disease.

Past Illnesses. Unimportant.

Family History. One sister has diabetes complicated with gangrene.

Physical Examination. The positive findings were: Height, 64 in.; nutrition good; pupils respond sluggishly to light; marked cyanosis of both legs and feet when in the dependent position, with prompt blanching when elevated and no dorsalis pedis or posterior tibial pulsations in either foot.

Laboratory Data. The blood serological tests and the counts were normal. The Roentgen ray examination revealed extensive calcification of the arteries of both feet and the electrocardiogram showed evidence of myocardial disease.

Progress Notes. On September 30, after 1 week on a weighed diet (70 gm. protein, 106 gm. fat and 90 gm. carbohydrate—1594 calories), the blood sugar being normal and no glycosuria being found, daily increases of 15 gm. of carbohydrate and the corresponding 60 calories were begun with 1 gm. of duodenal extract (No. 3005889) t. i. d. before meals.

Judging from the glycosuria on admission (it is to be noted that this patient was on the same diet, though estimated, for 4 months prior to admission), it was surprising to find no glycosuria or hyperglycemia when the carbohydrate reached 165 gm. and the total calories 1894 after 5 days of duodenal extract therapy. At this point a glucose tolerance test was given (Table 3). There was no glycosuria.

Further increases in the carbohydrate to 240 gm. on October 9 did not cause glycosuria or hyperglycemia. The diet was held at 70 gm. protein, 106 gm. fat and 240 gm. of carbohydrate (2194 calories) and the duodenal extract was stopped. No significant changes in the blood sugar followed.

On October 17 (7 days without the extract) the tolerance test was repeated. The curve was decidedly diabetic in type (Table 3) and there was glycosuria (1 gm.).

It seemed that with a practically normal curve previously, while he was receiving extract, and a pronounced diabetic type of curve without it that benefit had been secured. The carbohydrate and total calories of the diet were not the same when both tests were given however.

The extract was resumed on October 18; the diet was unchanged, and on October 30 (12 days after the extract was begun) the test was repeated. A decidedly better curve was obtained (Table 3).

On November 3 the diet was increased to 70 gm. protein, 80 gm. fat and 350 gm. of carbohydrate (2400 calories), and on November 6 the duodenal extract was stopped. On November 20 the glucose tolerance test resulted in a decidedly diabetic type of curve, with glycosuria—2.8 gm.

The patient was discharged on December 19, when the first diet (70 gm. protein, 106 gm. fat and 90 gm. of carbohydrate—1600 calories) was resumed. This diet was continued, and on February 2, 1934, another tolerance curve was secured. No extract had been used in the meantime. The curve was that of a pronounced diabetic. Sugar appeared in all 3 urine specimens.

The duodenal extract (No. 3026511) was resumed on February 8, 1 gm. t. i. d., and on February 14 the diet was increased to 70 gm. protein, 165 gm. fat and 110 gm. carbohydrate (2200 calories) and on February 20 the tolerance test was repeated. The curve registered a decided improvement and there was no glycosuria.

TABLE 3.—DATA IN THE STUDY OF CASE 3.

Date.	Tolerance curves, hours.					Duodenal extract.	Diet.				Wt., kg.
	F.*	½	1.	2.	3.		P.	F.	C.	Cal.	
1. Oct. 5	110	178	174	155	103	Begun Sept. 30	70	106	165	1894	83
2. Oct. 17	100	138	167	165	179	Stopped Oct. 9	70	106	240	2194	83
3. Oct. 30	100	..	166	161	117	Resumed Oct. 17	70	106	240	2194	83
4. Nov. 20	115	..	205	200	194	Stopped Nov. 6	70	80	350	2400	82
5. Feb. 2	129	..	169	..	242	None since Dec. 5	70	106	90	1600	80
6. Feb. 20	89	..	149	170	118	Resumed Feb. 4	70	165	110	2200	80

* Fasting.

SUMMARY OF CASE. While the duodenal extract was being given to a known diabetic increases in the carbohydrate and total calories to the level of a normal diet were made without causing hyperglycemia or glycosuria.

Three tolerance curves, 1, 3 and 6, obtained while the extract was

being given, were all decidedly better than the curves 2, 4 and 5, which were obtained at varying periods after the extract had been withdrawn.

CASE 4.—A. B. (Jefferson Hosp. No. WH8386), a girl, aged 13, was admitted to Dr. McCrae's Service on March 31, 1934, complaining of weakness, thirst, poor vision, excessive appetite and frequent urination.

Family History. Negative.

Past Illnesses. Measles in childhood and frequent "sore throats" prior to removal of her tonsils, in 1929. She has never menstruated.

Present Illness. In January, 1934, she noticed an excessive appetite, increased thirst and weakness. In February, polyuria and pruritus vulvæ and in March a blurring of vision became troublesome. On March 15, a physician was consulted; a diagnosis of diabetes was made; a diet was outlined and the patient was improved subjectively. She was referred to the hospital for observation.

Physical Examination. Appears drowsy, cheeks flushed, skin dry with a scabetic eruption on face and chest, faint odor of acetone on breath, posterior cervical glands palpable, breath sounds moderately harsh and with impaired resonance over the first intercostal space anteriorly, patellar and Achilles reflexes absent, and a fine tremor of the extremities.

Further Studies. Roentgen ray examination, April 14, showed numerous exudative deposits scattered throughout both lungs, believed by Dr. Farrell to be active tuberculous lesions; tuberculin test strongly positive; gastric contents, stools and smears from the pharynx negative for acid-fast bacilli; no sputum obtained; fractional gastric analysis and blood counts normal; Roentgen ray examination, on May 24, revealed no essential change while one on August 17 showed that many of the exudative deposits had disappeared but that characteristics of tuberculous infection remained. The body temperature fluctuated between normal and 100.6° F.

Progress Notes. (See Table 4.) A blood sugar on admission of 0.258%, a heavy reaction for sugar, acetone and di-acetic acid in the urine, the acetone odor to the breath, the age of the patient and her drowsiness from ketosis made insulin treatment imperative. Eighty units daily, in 4 doses, were needed.

On April 7, while 80 units of insulin were being given, the duodenal extract (No. 3026853) was begun, 0.5 gm. before meals and at bedtime. A rapid reduction in the insulin was made.

On April 14 the insulin was discontinued. The blood sugar was 0.086% on the morning following the last day of the insulin program, yet on April 16, 2 days without insulin, it was 0.080%.

The diet was increased abruptly on April 17 to 65 gm. protein, 82 gm. fat and 150 gm. carbohydrate (1600 calories), an increase of 5 gm. protein, 22 gm. fat and 60 gm. carbohydrate (460 calories). The blood sugar increased from 0.080% to 0.110% and on April 20 to 0.134%. On April 20 the diet was decreased to 65 gm. protein, 125 gm. carbohydrate and 82 gm. fat (1500 calories), which was still considerably higher than that allowed at the outset of treatment.

The glycosuria ceased and normal blood sugar values were restored.

On May 7 the diet was increased to 65 gm. protein, 135 gm. carbohydrate and 100 gm. fat (1700 calories), and on May 10 the extract was stopped. Neither glycosuria or hyperglycemia resulted. Further increases in diet were made on May 12 and June 12, making the diet 2272 calories. Daily increases of 10 gm. carbohydrate and 40 calories were begun on June 25 and continued until July 8, when the former had reached 295 gm. and the latter 2832. The blood sugar was 0.129% on July 6, following a diet of 80 gm. protein, 265 gm. carbohydrate and 148 gm. fat (2712 calories).

Glycosuria was noted when the carbohydrate reached 295 gm. and the blood sugar reached 0.179%. No extract had been given since May 10.

On July 9 the former diet (80 gm. protein, 155 gm. carbohydrate and 148 gm. fat—2272 calories) was resumed—a sudden decrease of 140 gm. carbohydrate and 560 calories. The blood sugar decreased slightly but subsequently increased to 0.190%—actually higher than with the high carbohydrate, high calorie diet—and there was glycosuria. The effect of the extract was doubtless exhausted.

The duodenal extract (No. 3041362) was resumed on July 9, but it had no effect on the hyperglycemia. Insulin was begun on July 25; 67 units were needed with the low diet to correct the hyperglycemia. This is in contrast to the blood sugar of 0.091% on July 3, seemingly maintained by the extract with a diet of 80 gm. protein, 235 gm. carbohydrate and 148 gm. fat (2592 calories).

The insulin having reduced the blood sugar to normal was stopped. The blood sugar was 0.121% the last day of insulin treatment, while after 1 day without 67 units of insulin it was lower, 0.113%, and after 3 days it was 0.116%.

When readmitted for a repetition of the study, in November, 1934, this patient's insulin requirement was between 60 and 70 units and tubercle bacilli were found in the gastric contents.

TABLE 4.—DATA IN STUDY OF CASE 4.

Date, 1934.	P., gm.	F., gm.	C., gm.	Total Cals.	Insulin units.	Duodenal extract.	Blood sugar.	Glycosuria.
4/ 1–4/ 7	60	60	90	1140	20–80	0	258–156	29.7–0
4/ 8–4/16	60	60	90	1140	75–0	½ gm. q.i.d.	117–86	0.0–0.2
4/17–4/19	65	82	150	1600	0	"	110	0.5–3.7
4/20–5/ 6	65	82	125	1500	0	"	154–76	5.8–0
5/ 7–5/10	65	100	135	1700	0	"	99	0.0–0
5/11	65	100	135	1700	0	0	...	0.0–0
5/12–5/28	65	124	135	1916	0	0	85–105	0.0–0
5/29–6/11	70	138	145	2100	0	0	112–99	0.0–0
6/12–6/24	80	148	155	2272	0	0	98–112	0.0–0
6/25–7/ 8	80	148	165–295	2312–2832	0	0	91–129	0.0–0
7/ 9–7/24	80	148	155	2272	0	½ gm. q.i.d.	138–179	16.0–0
7/25–8/ 4	80	148	155	2272	40–67	"	190–105	8.0–0
8/ 5–8/11	80	148	155	2272	0	"	113–121	0.0–0

Weight increased gradually from 38 to 41 kg. Height, 61 inches.

CASE 5.—C. B. (Penn. Hosp. No. 8897), a colored woman, aged 50, was admitted to the hospital on May 24, 1934, complaining of loss of vision in the right eye, cough and vague abdominal pain.

Family History. A distant cousin had diabetes, otherwise unimportant.

Past History and Present Illness. She has used sweets freely and tobacco in moderation. She had 1 stillborn child, 2 miscarriages and 1 living child. In January, 1934, following an acute upper respiratory tract infection, a cough, which has remained, became troublesome; she had pains, made worse by coughing, over her right upper chest; small amounts of mucopurulent material were expectorated at night. An attack of pleurisy last winter affected the left chest. Thirst, polyuria, nocturia and pruritus vulvæ were troublesome for 2 or 3 years, while dyspnea on exertion, anorexia, general weakness, failing vision and marked tingling and burning sensations in the toes have been noted recently.

Physical Examination. Bilateral cataracts (right nearly mature), few carious teeth, tongue heavily coated, breasts atrophied, limitation of expansion over the right upper chest, a dull note on percussion over the upper lobe, with high-pitched breath sounds, egophony, whispered pectoriloquy, with fine and medium crackling râles anteriorly and posteriorly over the same area, abdominal wall flaccid, a palpable mass the size of a medium grapefruit in the suprapubic region (uterine fibroma) and the blood pressure 98/50

Further Observations. The blood serological tests were normal, the Roentgen ray study of the chest revealed multiple cavitations involving the entire upper right lobe, many acid-fast bacilli were found in the sputum, and blood count was: Hemoglobin, 75%; red blood cells, 5,860,000; white blood cells, 11,150; with a normal differential count, and the gastric analysis was normal.

Progress Notes. The fasting blood sugar was 0.165% on May 22 and 0.162% on May 25, and there was heavy glycosuria (2%). A diet of 1380 calories was allowed.

The patient's temperature varied from normal to 102° F. The fluctuations were slightly less toward the end of the study. Unfortunately the quantitative tests for sugar were not done before May 29, but judging from the qualitative tests there was no decrease in the glycosuria while the treatment was by diet alone. From May 25 to 31, heavy glycosuria persisted, 24.4 gm. on May 29. In view of the tuberculous infection, the febrile course, the decreasing weight, the increasing blood sugar and the glycosuria, insulin therapy was considered imperative. It was begun on May 30 and continued until June 7. The diet was increased on May 31 to 1600 calories, the insulin was increased to 30 units and duodenal extract (No. 3041362), 0.25 gm. q. i. d., was begun. The blood sugar was 0.209% and there was glycosuria, 4.7 gm.

June 1 to 7, the insulin was increased to 36 units daily, the blood sugar was 0.129% and there was no glycosuria. On June 7 the insulin was stopped. No glycosuria ensued and the blood sugar decreased to 0.110%. The weight remained constant.

The diet was increased on June 13 to 2000 calories. A temporary increase in the blood sugar to 0.135% ensued, but normal values were restored on June 20 and 22. The duodenal extract was stopped on June 22. There was no resulting increase in the blood sugar.

Daily additions of 10 gm. of carbohydrate and 40 calories to the diet were begun on July 6 to determine the limit of tolerance. The blood sugar was 0.110%, July 6 to 17, being 0.110% on July 10, when the diet contained 165 gm. of carbohydrate and 2200 calories. On July 14 the blood sugar was 0.129%, when the diet contained 205 gm. carbohydrate and 2360 calories. Further elevation of the blood sugar to 0.143% occurred on July 18, when the carbohydrate value reached 235 gm., and the calories 2480 on the day previous. Traces of sugar were found in the urine on July 12 and 16.

The duodenal extract was resumed, 0.25 gm. q. i. d., on July 17. July 18 to 24, the former diet (2000 calories), was resumed. Despite this reduction (120 gm. of carbohydrate and 480 calories) plus the use of insulin (resumed, July 19), the blood sugar was higher, 0.166%, on July 21. It was 0.143% on July 23 and 0.153% on July 24. There was, therefore, no decrease in the blood sugar during the 6 days, July 19 to 24, while 36 units of insulin were given daily in 3 doses. The duodenal extract had no apparent effect during this period. July 25 to 31, no insulin was given or subsequently. The blood sugar on July 27 was lower, 0.139%, than when insulin was used. It was 0.139% and 0.137% on July 30 and 31, respectively.

TABLE 5.—DATA IN STUDY OF CASE 5.

Date, 1934.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
5/21–5/29	70	80	95	1380	None	None	162–165	Heavy
5/30	70	80	95	1380	15	None	...	20.7
5/31–6/ 6	70	104	95	1600	30–36	¼ gm. q.i.d.	209–145	4.7–0
6/ 7–6/12	70	104	95	1600	None	¼ gm. q.i.d.	129–110	0
6/13–6/21	70	140	115	2000	None	¼ gm. q.i.d.	135–113	0
6/22–7/ 5	70	140	115	2000	None	None	112–109	0
7/ 6–7/17	70	140	125–235	2040–2480	None	None	110–129	Trace
7/18–7/24	70	140	115	2000	36	¼ gm. q.i.d.	143–166	0
7/25–7/30	70	140	115	2000	None	¼ gm. q.i.d.	137–139	0

The weight at the onset was 55½kg. and on discharge 54 kg.; height, 63½ inches.

SUMMARY OF CASE. 1. During the 8 days of insulin treatment the blood sugar fell from 0.209% to 0.129%. This occurred while insulin and duodenal extract were being given.

2. When the insulin was abruptly stopped further decrease in the blood sugar occurred, to 0.110%, presumably due to the effect of the duodenal extract. This effect was repeated during the later stages of the study, when 36 units of insulin were stopped, July 24, the blood sugar fell to a lower level than when the insulin was being given.

3. No glycosuria or hyperglycemia resulted from stopping the duodenal extract.

4. Remarkable increases in the carbohydrate and total calories were necessary to provoke hyperglycemia and glycosuria even though the extract had been stopped.

5. Despite a resumption of the previous lower diet plus insulin there was a continued rise in the blood sugar suggesting that the hyperglycemia had destroyed the effect of the extract or, as seems more likely judging from other cases, its effect was in abeyance while insulin was given.

CASE 6.—A. S. (Penn. Hosp. No. 26668), male, Italian, aged 49, was admitted on September 23, 1933. A history of diabetes since 1927 was given when, because of increased thirst and appetite, he had consulted a private physician who found glycosuria. Until his admission, in July, 1932, for treatment of diabetes and a large carbuncle on his back, treatment has been spasmodic.

After his discharge, in 1932, he was treated in the Out-Patient Dispensary save for 7 admissions for treatment of carbuncles.

Past Illnesses and Family History. Unimportant.

Physical Examination. Well nourished; blood pressure, 135/80; multiple scars over chest, back and neck where carbuncles had been incised. The heart, lungs and abdomen were normal.

Laboratory Studies. Blood serological tests normal; red blood cells, 3,320,000; hemoglobin, 85%. Roentgen ray examination of the extremities revealed a moderate degree of calcification of the arteries of both legs.

Progress Notes. A history of heavy glycosuria and several blood sugar estimations above normal, the highest being 0.230%, in July, 1932, made it obvious that he had diabetes.

He was given a diet containing 1600 calories, with 110 gm. of carbohydrate on September 23, 1933, and on September 26 daily increases of 10 gm. of carbohydrate and 40 calories were begun and the duodenal extract (No. 3005889), in doses of 2 gm. t. i. d., was started.

There was no glycosuria or hyperglycemia when the carbohydrate reached 260 gm., and the total calories 2187, but a glucose tolerance test (October 5) indicated a very mild diabetes. The diet was then abruptly increased, allowing 350 gm. of carbohydrate and 2557 calories. The blood sugar remained normal.

The extract was stopped on October 9, but the tolerance curve on October 24 suggested that its effect was still operating. The curve might well be interpreted as normal (Table 6) and there was no glycosuria.

On October 30, 100 gm. of glucose were given to this patient by mistake. While no blood tests were made, it is interesting that 6 gm. of sugar were lost in the urine, 34 days after stopping the duodenal extract. Glycosuria had not occurred with the preceding glucose tolerance tests. This contrast may be misleading, as there was at this time a small carbuncle developing on the patient's back. This was freely incised on November 2.

To prevent unnecessary risk the diet was decreased to 1050 calories, with 150 gm. carbohydrate for 7 days, insulin was given and the duodenal extract was resumed. During the course of this infection there was glycosuria and the blood sugar reached 0.205%.

It is perhaps significant that later, March 1 to 19, 1934, a much larger carbuncle appeared during a course of duodenal extract therapy without this apparent loss of tolerance. The diet which had contained 2100 calories, with 175 gm. carbohydrate, from January 20, was left unchanged; no insulin was given but the extract was continued. In this instance the highest blood sugar, the only one above normal, was 0.135% and there was no glycosuria.

On January 15, 1934, 63 days without the extract, and with a smaller diet a poorer tolerance curve was obtained. The blood sugar increased between the 1st and 2d hours and it was above normal at the 3d hour.

On January 22 (70 days without extract) a still poorer curve was obtained. The increase in blood sugar between the 1st and 2d hours was greater, the peak was 0.201% at the 2d hour and the 3d hour blood sugar was 0.174%, the highest 3d-hour value yet obtained.

The duodenal extract (No. 3026511) was resumed on January 22, and on January 31 the glucose tolerance test showed a definite improvement over that of January 22. The peak was lower, the blood sugar remained at practically the same level between the 1st and 2d hours and the 3d hour blood sugar was 0.138%.

On April 10 (after 45 days of extract therapy) further improvement was noted. The curve had its peak at the 1st hour, a greater fall between the 1st and 2d hours and a normal figure at the 3d hour.

The changes which were made in the diet cannot account, we believe, for the curves obtained, neither can the small changes in weight. As for the carbuncles they appeared at such times as to make proof of the effectiveness of the extract most difficult. Especially valuable in our estimations is the curve on April 10, as a very large carbuncle causing fever for several days had intervened between this and the date of the previous test, on January 31.

He was discharged on June 2 and received no extract after June 18. He was readmitted, for a repetition of the study, on November 19, 1934. There was no glycosuria or hyperglycemia nor was there a recurrence of the carbuncles in the interval.

TABLE 6.—DATA IN STUDY OF CASE 6.

Date.	Diet.				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
1932.								
7/20–8/5	70	40	120	1120	30–36	None	230–100	Heavy–0
1933–1934.								
9/23– 9/25	80	93	110	1600	None	None	114	0
9/26–10/ 6	80	93	125	1657	None	2 gm. t.i.d.	75–92	0
			350	2557				
10/ 7–10/ 9	80	93	350	2557	None	2 gm. t.i.d.	82	0
10/10–11/ 1	80	93	350	2557	None	None	77–189	
11/ 2–11/ 8	65	21	150	1050	6–24	1 gm. t.i.d.	82–205	18–6
11/ 9–11/29	80	93	350	2557	None	1 gm. t.i.d.	68–95	Trace–0
11/30–12/ 7	80	93	350	2557	None	2 gm. t.i.d.	83	0
12/ 8–12/14	75	153	105	2100	None	None	...	0
12/15– 1/21	75	122	175	2100	None	None	101–119	0
1/22– 4/12	75	122	175	2100	None	1 gm. t.i.d.	75–135	0

The weight increased gradually from 63 to 68 kg. Height, 65 inches.

Glucose tolerance tests on November 27 and December 4 were considered normal. There being no object in resuming the extract under these conditions, he was discharged on December 5.

Glucose Tolerance Tests.

Year.	Date.	Hours. F.	½.	1.	2.	3.
1933	October 5	84	130	168	154	53
"	October 24	80	...	161	122	82
1934	January 15	119	...	173	184	157
"	January 22	101	...	161	201	174
"	January 31	91	...	155	157	138
"	April 10	82	...	183	123	105
"	November 27	118	188	134	111	75
"	December 4	122	135	188	94	98

SUMMARY OF CASE. The duodenal extract seemed to produce better tolerance curves than were obtained without it, and it seemed to prevent the usual loss of tolerance during an acute pyogenic infection. Furthermore, normal glucose tolerance curves were obtained 5 months after stopping the extract. This patient received extract for a longer period than any other.

CASE 7.—G. D. (Penn. Hosp. No. 33529), female, aged 8, was admitted on February 19, 1934, complaining of excessive appetite and thirst, polyuria and loss of weight.

Family History. Unimportant.

Past History. Mumps at 6, scarlet fever and chickenpox at 7, with "ear trouble without discharge" for several days. She had enuresis until the age of 4, and subsequently increased urination with nocturia, nervous-

ness and occasional fleeting pains in the right lower quadrant of the abdomen. Urinalyses done in 1933 were normal.

Present Illness. She was well until 3 weeks before admission, when polyuria was noticed. A great appetite and excessive thirst developed and a rapid loss in weight ensued. The urine became syrupy and when dried on clothing left crisp areas. Dr. H. Haines, consulted on February 14, found glycosuria. Improvement followed the adoption of a restricted diet.

Physical Examination. Patient undernourished, moderate enlargement of the tonsils and submaxillary glands, posterior cervical gland (right) palpable, heart and lungs normal, small pad of fat in center of the abdomen and blood pressure 105/70.

Laboratory Data. Blood sugar 0.203% and urine sugar 4+ (72 gm. in 8 hours). The blood urea and blood counts were normal. The tests for acetone and di-acetic acid in the urine were strongly positive.

Progress Notes. It was obvious at the outset that this patient needed insulin, but we wished to observe the effect of the duodenal extract on the hyperglycemia of a child who had never received insulin. The extract was begun at once (No. 3026511 for the first day and No. 3031959 subsequently), in doses of 1 gm., before each meal.

Though the glycosuria decreased, the blood sugar increased to 0.210% and on February 23 to 0.230%. No benefit from the extract being apparent in the first 3 days, insulin was begun.

On February 24 (5 days after admission) the patient had fever, 99.6° F. The temperature remained elevated, during an attack of measles, until March 1. At the height of the fever, 48 units of insulin, given in 4 doses, reduced the blood sugar to 0.098%. A higher dosage, 56 units, was given after all fever had subsided without any evidence of insulin reactions. In view of the prompt gain in tolerance which usually follows the disappearance of fever, we suspected that the extract might be exerting an influence against hypoglycemic reactions in this patient.

On the morning of March 10, a blood sugar of 0.111% was found and the insulin was stopped, an abrupt withdrawal of 56 units. Slight glycosuria occurred until March 16. There was no further loss and the blood sugar values remained normal.

The diet was increased on March 20 and a gradual gain in weight ensued. The patient was discharged on March 24.

The extract was stopped on April 3 and glycosuria appeared on April 24, May 3 and 4. The extract was resumed, 0.5 gm. t. i. d., for 1 week. There was no glycosuria. As it seemed that there was a delayed benefit from the extract lasting from April 3 to 24 we decided to give the extract for 1 week in each month.

From May 5 to 10, inclusive, the extract was given, 0.25 gm. q. i. d., and again from June 1 to 7, inclusive. The blood sugar remained normal and there was no glycosuria. On June 25, 26 and 27, glycosuria appeared but subsided when the extract was resumed, July 1 to 7. Being without active extract we were specially interested in subsequent observations.

Glycosuria returned on July 22 and the blood sugar increased to 0.139% on July 26. Insulin was resumed on August 10; the blood sugar reached 0.239% on September 21 and the insulin requirement has (February, 1935) reached 46 units. A repetition of the study is under way.

SUMMARY OF CASE. 1. Judging from her age, weight and laboratory studies, before and after using the extract, the child obviously had a severe diabetes of recent onset. This was apparent before the measles could have altered the picture.

2. We regard it as significant for a child of her physique needing so much insulin during a febrile period to tolerate an actual increase

in the dosage after the disappearance of fever without insulin reactions.

3. There was no demonstrable effect from the extract during the initial 3 days, but later a delayed effect, made possible by the control of the diabetes, seemed to assert itself in an insulin-like action by which it corrected the glycosuria and maintained a normal blood sugar in a patient in whom this would be considered possible only with insulin. The full effect of the extract was not apparent until 6 days had elapsed without insulin.

4. The effect of the extract seems to have lasted, in this patient, about 3 weeks after its discontinuance.

TABLE 7.—DATA IN STUDY OF CASE 7.

Date, 1934.	Diet				Insulin, units.	Duodenal extract.	Blood sugar.	Glycosuria, gm.
	P.	F.	C.	Cal.				
2/19– 2/22	45	53	110	1100	None	1 gm. t.i.d.	203–210	72 0–51 6
2/23– 3/ 9	45	53	110	1100	32–56	1 gm. t.i.d.	230–98	6 7–0
3/10– 3/19	45	53	110	1100	None	1 gm. t.i.d.	85–103	3 8–0
3/20– 4/ 3	60	87	120	1500	None	1 gm. t.i.d.	91–112	0–0
4/ 4– 5/ 4	60	87	120	1500	None	None	105–123	0–trace
5/ 5– 5/10	60	87	120	1500	None	1 gm. q.i.d.	111–119	0
5/11– 5/31	60	87	120	1500	None	None	102–129	0
6/ 1– 6/ 7	60	87	120	1500	None	½ gm. q.i.d.	...	0
6/ 8	60	87	120	1500	None	None	112	0
6/ 9– 6/30	65	87	130	1560	None	None	129	0–trace
7/ 1– 7/ 7	65	87	130	1560	None	1 gm. q.i.d.	114	0
7/8 –11/30	65	87	130	1560	14–28	None	72–239	0–heavy

Weight increased gradually from 27.2 to 31 kg. Height, 54 inches.

Summary and Hypothesis. A child diabetic of 8, another of 13, with active tuberculosis, an adult with active tuberculosis, another admitted in coma, a boy of 16 admitted in impending coma and 2 mild diabetics of the arteriosclerotic group (7 cases in all) are presented to illustrate that the duodenal extract prevented hyperglycemia and glycosuria of any extent after the withdrawal of large doses of insulin and that subsequent great increases of carbohydrate and calories were necessary to produce hyperglycemia and glycosuria. Furthermore, better glucose tolerance curves were obtained with the extract than were obtained without it.

The period of benefit following the withdrawal of the extract varied from a few days to several months.

There is no evidence that the extract is of value in reducing a marked hyperglycemia or that it has any effect when given with insulin, except as stated below, but rather that its effect becomes discernible when insulin is used to control the diabetes and then omitted. Repeatedly, lower blood sugar values were obtained with the extract alone than when it was given in conjunction with insulin.

In 2 patients (1 of whom is reported here) with diabetes of long

standing normal glucose tolerance curves were repeatedly obtained 5 months after cessation of extract therapy.

Neither hypoglycemic reactions nor any other untoward effect were noted. It seemed rather that the extract exerted an anti-hypoglycemic effect when large amounts of insulin were given.

Respiratory quotient studies (not reported here) coincided with the behavior of the blood and urine sugars, increasing as they decreased and decreasing as they increased.

Doses of 0.25 gm. of the extract, given orally, 3 or 4 times daily, were effective.

Of 46 patients who received the extract, 16 were given inert material. Of the remaining 30, 12 had severe and 18 had mild diabetes. Of the 12 with severe diabetes, 8 (4 of whom were children) showed a definite response to extract therapy, while 4 (3 adults and 1 girl of 16) gave no evidence of benefit. Of the 18 mild cases, 11 were helped and 7 were not.

All 4 of the severe diabetics who failed to benefit from the extract belong to the group of diabetics who have an extremely narrow margin of safety between hypoglycemia and hyperglycemia. Other severe diabetics requiring as much or more insulin, but who had a greater margin of safety, gave spectacular response to extract therapy.

The results suggest that 3 types of diabetes exist, *e. g.*, (1) from lack of activation of the pancreatic islands by a duodenal factor, (2) from loss of islands of Langerhans and (3) an insensitiveness of the organism to insulin. The last mentioned may be subdivided to include various endocrinal imbalances.

The prolonged period of apparent benefit after withdrawal of the extract suggests the possibility that the duodenal factor is to the pancreas as iodin is to the thyroid gland. This tentative hypothesis is presented for consideration until we are obliged to alter or add to it in the face of new evidence obtained by a continuation of our study.

The authors are grateful to Parke, Davis & Co., especially to Dr. A. E. Sharpe of their staff, for supplying us with the duodenal extract. We are indebted to Drs. Macallum and Laughton for making the animal assays for us and for their readiness to place at our disposal the results of their studies on this subject. We wish to express our appreciation to the staffs of the Pennsylvania and Jefferson Hospitals, who aided in carrying out this study.

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NOTE ON THE USE OF SUPRARENAL EXTRACT AND SODIUM SALTS IN A CASE OF ADDISON'S DISEASE.

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Productive research during the past few years has done much to revive interest in the study of Addison's disease, and to elucidate some of its problems. Swingle and Pfiffner,[1] and Hartman[2] have prepared extracts of the cortex of the suprarenal glands which are effective in maintaining the lives of adrenalectomized dogs and have proved of value in treatment of certain human cases. Loeb[3] and Harrop[4] have shown a relationship between sodium chlorid loss from the body and the development of Addisonian crises. Loeb[5] believes that the most satisfactory hypothesis to explain the behavior of the sodium base in suprarenal insufficiency is that the suprarenal glands exert a regulatory effect on sodium excretion.

The following case of Addison's disease is reported because of two points: (1) The failure of cortical extract alone to prevent the development of crisis; and (2) the demonstration that other sodium salts can be substituted for sodium chlorid without detriment.

Case Abstract. The patient, aged 25, was sent to the Lakeside Hospital on September 9, 1933, by his family physician because of Addison's disease. This diagnosis was manifest because of conspicuous darkening of the skin, vomiting, weakness and weight loss, all coming on in a period of 3 months. No history of exposure to tuberculosis could be elicited. Past illness was negligible (acute gonorrhea in 1930; measles, diphtheria and influenza in childhood). Four months before admission, he was ill with dry pleurisy for 3 days. He was native born of Polish parents, single, unemployed for 2½ years, formerly a welder.

Physical examination showed nothing significant except pigmentation and a blood pressure of 108/55. The skin was uniformly dark grayish-brown with darker spots, 2 mm. in diameter, over each cheek, hard palate, gums, buccal mucous membrane and in the conjunctiva of one eye. A few days later similar spots developed on his forearms and later disappeared while under treatment. Temperature averaged 37.5°, pulse 80 and respirations 22.

The urine was normal except for a low specific gravity (1.012). Hemoglobin (Sahli) 91%, erythrocytes 5,150,000 and leukocytes 8400. The blood smear was normal and the blood Wassermann test negative. Blood sugar 75, plasma chlorid 310 and creatinin 1.5 mg.%. Icteric index 6.

Basal metabolic rate −2% of normal. Electrocardiogram normal. Roentgen ray of lungs showed no evidence of old or recent tuberculosis. A plate of the abdomen showed several flaky areas overlying the upper pole of the left kidney. These had the density of calcium salts, and it was believed might represent changes within the adrenal. There were no similar shadows on the right.

Our plan to study his salt metabolism was hurried by a mild crisis. He had been given a full diet, and allowed to salt his own food. On the third hospital day, he suddenly became irrational and vomited repeatedly. His temperature was unchanged, but his blood pressure fell to 80/40. He was given 750 cc. of physiologic salt solution intravenously, with temporary improvement. His chlorid (as Cl) intake the preceding day had been 2.53 and urinary output 3.24 gm.; on this day intake was 4.21 and output 4.03 gm. The following day he again became irrational and vomited. The blood urea nitrogen was 23.6 and plasma chlorids 270 mg.%. He was given 2250 cc. saline solution subcutaneously and intravenously. On the fifth hospital day he was markedly improved, and eating well.

Since it was obvious that he could not keep himself in salt balance by his diet, however salty, he was given additional salt—finally 12 gm. NaCl daily—in capsules. With this additional intake of salt, he ate well and had no complaints. On the ninth night, in a "nightmare" he fell out of bed, breaking a glass urinal and cutting his thigh on a large fragment. This kept him in bed until the twenty-second hospital day, when he felt well enough to walk about the ward. Without sudden change, his blood pressure had come up to 110/75. During this period, his chlorid (Cl) intake, including the calculated amount in his food and that in the weighed amount of NaCl on his trays and in the capsules, varied from 6.66 to 18.06 gm. daily, and his urinary output from 5.22 to 16.8 gm. There was no significant change in weight. Hemoglobin 90%, erythrocytes, 5,200,000 and leukocytes 8100. Blood urea nitrogen was 19.7 and plasma chlorids 335 mg.%.

On the twenty-fourth hospital day, the salt capsules were stopped, but an abundance was provided with his meals which were generous, for he was feeling well. The following day he was "despondent," the next irritable and remained voluntarily in bed. His appetite was fair, and blood pressure 110/75. On the fifth day without capsules he was worse mentally and was nauseated. His chlorid intake on these days had been 8.5, 6.4, 5.37, 3.09 and 4.87 gm.; his output, 10.81, 10.41, 9.14, 6.6 and 5.45 gm. A crisis was obviously developing, but his blood pressure was 105/80, pulse and temperature normal, fluid intake 1750 cc. and output 1150 cc. There was no demonstrable trouble with his circulation, no water loss or retention and no sign of disordered central nervous system. The blood sugar was 99, urea nitrogen 25.4 and plasma chlorids 317 mg.%. It was then impossible to predict the crisis from any physiologic change, but it was quite apparent to the many observers familiar with his previous behavior that a crisis was impending.

Two days later—on the eighth day after the salt capsules had been stopped—he was clearly in crisis, as shown by low blood pressure (85/55), vomiting, blood urea nitrogen 30.3 and plasma chlorids 292 mg.%. He was given 30 cc. of a potent suprarenal cortex extract* intravenously during the day, and food and drink with and without salt were urged. There was no improvement. The next day he received 30 cc. eschatin intravenously and 30 cc. intramuscularly without improvement. Since he was getting worse, it was thought dangerous to trust to eschatin alone any longer. He was, therefore, given glucose and saline solution intravenously, with definite improvement in 12 hours and great improvement in 36 hours. He

* Eschatin—Parke, Davis & Co. Furnished through the courtesy of Dr. E. A. Sharp.

was then put back on a full diet with 12 gm. NaCl in capsules daily. The events of this period are shown in Table 1.

TABLE 1.—EFFECT OF ESCHATIN AND NaCl DURING A CRISIS.

Hospital Day.	Cl intake, gm.	Cl urine, gm.	Blood sugar, mg. %	B.U.N., mg. %	Plasma Cl, mg. %	Hgb., %	R.B.C., millions	W.B.C., thousands	Remarks.
25th	6.40	10.40	76	19.7	335				Second day without NaCl capsules.
29th	1.09	3.19	99	25.4	317	90	5.2	8.0	Sixth day without NaCl capsules.
30th	?	5.06	..	..	..	..	..	..	Crisis impending.
31st (8 A.M.)				30.3	292				Before eschatin.
(9 P.M.)	?	1.09	79	28.0	283	103	5.8	9.6	In crisis: After 30 cc. eschatin
32d (7 P.M.)	?	1.06	72	40.7	266				In crisis: After 80 cc. eschatin
33d	11.37	3.38	90	32.4	280				After 20 gm. NaCl.
34th	10.62	13.49	80	21.1	326	70	3.9	7.7	Much improved.
35th	9.85	15.38	90	13.9	327				Apparently out of danger.

Ten days after this crisis he was up and seemed quite well. All observers agreed that there was fading of the pigmentation of his skin and many of the millimeter-sized patches on his forearms, which had been recorded by mapping, were found to have disappeared. His blood pressure was 105/75.

We wished to study the effect of substituting other chlorids and other sodium salts for NaCl. Consequently, on the sixty-third hospital day, with the knowledge and consent of the patient, the NaCl capsules were stopped, and mixtures of ammonium, calcium and potassium chlorids substituted. On the third day of this medication, he complained of abdominal pain, nausea and vomited. His blood pressure fell suddenly to 90/50, and he was given intravenous saline solution, with good results. The changes in the acid base balance in his serum are shown in Table 2. The effect of of these chlorids can scarcely be estimated, since nausea and abdominal distress developed too soon to say that sodium loss was the cause. Later, while on a full NaCl intake, capsules of KCl were again followed by abdominal distress, but not crisis.

TABLE 2.—EFFECT OF DIFFERENT SALTS ON SERUM ELECTROLYTES.

Date, 1933.	Total base, m.eq.	Cl, m.eq.	CO_2, m.eq.	Protein, m.eq.	P_2, m.eq.	Base — Acid, m.eq.	pH.	Remarks.
Nov. 2	148.8	100.8	24.8	16.6	3.5	3.1	7.35	On 12 gm. NaCl daily + salt on food.
5	143.7	93.2	21.2	18.7	2.7	7.9	7.40	After 3 days low NaCl, high Cl.
Dec. 5	150.4	99.1	25.4	16.6	2.5	6.8	7.38	After 14 days high Na, low Cl.
9	149.2	100.0	27.3	17.3	2.7	1.9	7.41	After 2 days high NaCl.

After 14 days of a full diet plus 12 gm. NaCl in capsules, a mixture of Na_2SO_4, and Na_3PO_4 and Na_2CO_3 containing an equal amount of Na was substituted for the NaCl capsules and he was given a salt-poor diet. He was maintained on this régime for 17 days without discomfort, and with little or no change in his serum electrolytes. His chlorids (as Cl) intake and urinary output fell to less than 1.5 gm. daily. This satisfied us that he could be kept from crisis by other sodium salts as well as by NaCl. He was up and about the ward quite as a healthy, cheerful person. He had,

however, become weary of hospital life and asked for a vacation. He was allowed to go home December 10, on a full diet plus 16 gm. NaCl daily in capsules.

He returned to the Out-Patient Department by appointment, December 20, with a blood pressure of 120/80, feeling strong and with a good appetite. A week later, although he had continued to take the same amount of NaCl, his appetite was not as good and he had been sleepless; blood pressure, 98/65, pulse 84 and temperature 36.3° C. The clinic physician, who had been his ward physician, noted his behavior and thought he was about to have a crisis and sent him into the hospital.

On readmission, January 3, 1934, a general survey of his condition disclosed no new developments, except that his color was lighter and the pigmented spots less numerous. Contrary to expectation, he did not go into crisis but remained well on his salt capsules (16 gm. daily) in addition to a liberal diet. Careful studies of his behavior did show him to be irritable and "unhappy" at times.

After 7 days, we undertook to make further studies of his salt metabolism, but the evening of the first day on this new régime he was found irritable and confused in the night. Since this suggested the onset of crisis, our plans were changed, and he was given saline solution subcutaneously and intravenously, and glucose solution intravenously. The following day with a blood sugar 47 and plasma chlorids 434 mg.%, he was in profound crisis. Signs of bronchopneumonia—râles, dullness and bronchial breathing—became manifest. His temperature rose to 38.5° C., pulse to 120 and respirations 45. In spite of eschatin (20 cc.) and saline and glucose solution intravenously, he died that afternoon. Autopsy was not permitted.

This patient presented a typical picture of Addison's disease of the acute type, in all probability due to tuberculosis of the adrenal glands. In spite of the fact that the disease was advanced enough to lead to a crisis shortly after admission, he was maintained in fair condition for 4 months by NaCl alone, without cortical extract. In one crisis, exhibition of NaCl was sufficient to bring him out, while in a subsequent one, cortical extract alone, even in large doses, was ineffective. This is at variance with the report of Snell.[6] The objection might be raised that cortical extract was withheld too long. It was given as soon as the signs of impending crisis became manifest, at a time when we believe NaCl alone would have been effective.

He remained in good condition when other sodium salts were substituted for NaCl. This supports Loeb's suggestion that one of the phenomena of Addison's disease is an abnormal sodium metabolism. Chlorid intake can be greatly reduced without apparent detriment. It is interesting that in spite of the marked decrease in chlorid excretion—from 16.41 to 1.06 gm. per day on the low chlorid diet, there was little change in his serum chlorids or total base. Finally, in the presence of infection, signs of crisis developed for which all treatment was unavailing.

Summary. In a patient with typical Addison's disease clinically, a potent extract of the suprarenal glands alone was ineffective in the treatment of crisis. Other sodium salts could be substituted for NaCl without detriment.

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HISTOLOGIC CHANGES IN THE ADRENALS OF TUMOR-BEARING RATS.

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Areas of infiltrating cells have frequently been noted in this laboratory in the course of histologic examination of the adrenal glands and periadrenal fat of young male albino rats bearing the Walker rat tumor, a transplantable malignant tumor of mammary origin which has been regarded as a carcinosarcoma. Similar areas of infiltration have been encountered in a variety of pathologic conditions, including cancer, in man (Paunz[1]).

In the adrenal medulla the infiltrating cells are composed of leukocytes and lymphocytes (Fig. 1), although they sometimes consist exclusively of eosinophilic leukocytes. These cells appear in large numbers within the medullary veins, but are still more frequently found in the neighborhood of the vessels, between the epithelial cells. Occasionally we have observed small homogeneous basophilic granules, which we regard as degenerated lymphocytes.

The same cellular elements are encountered in the adrenal cortex (Fig. 2), in a still larger proportion of glands examined. In this region we have also found accumulations of epithelioid cells, very similar to the adrenal cortical cells except in that they possess a decidedly basophilic cytoplasm. In some cases, infiltrating cells were also found in the periadrenal tissue, the spleen and the liver.

Areas of infiltration have been observed in approximately one-third of a total series of over 130 rats bearing this tumor; since serial sections were not made, the incidence may be higher. These areas, which never occur in normal rats, were not observed in animals which were sacrificed when the primary tumor weighed less than 50 gm. It is, therefore, quite possible that they represent a reaction to necrotic processes occurring within the larger tumors, rather than to the malignant growth as such. This was all the more

likely, since we were able to show in a previous communication that the changes occurring in the pituitary gland of tumor-bearing rats which have been considered as characteristic of cancer are simply the result of tissue decomposition.[2]

In order to test this theory we implanted 10 adult male albino rats, of the same age as those used in the tumor experiments, with fresh kidneys, taken from other albino rats. These implants were made under sterile conditions intraperitoneally at intervals of 3 to 10 days during a period of 49 days; the animals were then killed. Each of them received 12 kidney implants during this period. Although postmortem examination showed that the implanted kidneys were necrotic and had been largely absorbed, and the animals all showed the characteristic histologic changes in the hypophysis which we described in our previous paper, none of them had areas of infiltration in the adrenals. We have to conclude, therefore, that the formation of these areas in the adrenals of the tumor-bearing rat is not ascribable to the factor which produces the characteristic changes in the hypophysis. Since, on the other hand, such areas may very rarely be seen in the adrenals of chronically infected rats, we are not inclined to consider them as characteristic of the presence of living neoplastic tissue.

This view is also substantiated by another experimental series of 12 non-tumor-bearing rats, which were injected (6 subcutaneously and 6 intraperitoneally) twice daily with 2 cc. of necrotic tumor material prepared as follows: The peripheral zones of growing tissue were removed from large tumors weighing from 80 to 150 gm., the central portions, consisting almost entirely of necrotic cells, being placed in the freezer (−6° C.); after repeated freezing and thawing for 7 days, this necrotic tumor material was ground with sand, suspended in 3 volumes of 0.2% aqueous solution of sodium carbonate containing 0.25% tricresol, and centrifuged for 1 hour; the supernatant fluid was then decanted off for injection. These injections did not lead to the formation of tumors in any of the 12 experimental animals; 50% of them, however, developed abscesses at the site of injection and were accordingly sacrificed after 43 daily injections, the rest being treated for 58 days altogether. Histological examination revealed the presence of areas of infiltration in the adrenals in 3 cases, in the spleen in at least 7 cases, and in 1 case in the liver. Degenerative changes in the pituitary, similar to those observed in tumor-bearing rats,[2] were noted in 3 animals of this series.

Summary. Areas of infiltration of leukocytes and lymphocytes in the adrenal medulla and cortex of rats bearing the Walker rat tumor are described, and the possible causes of their formation are discussed.

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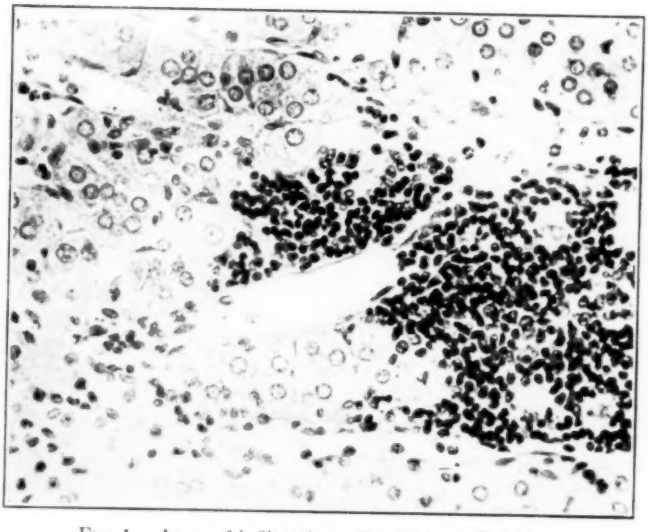

FIG. 1.—Areas of infiltrating cells within the medulla.

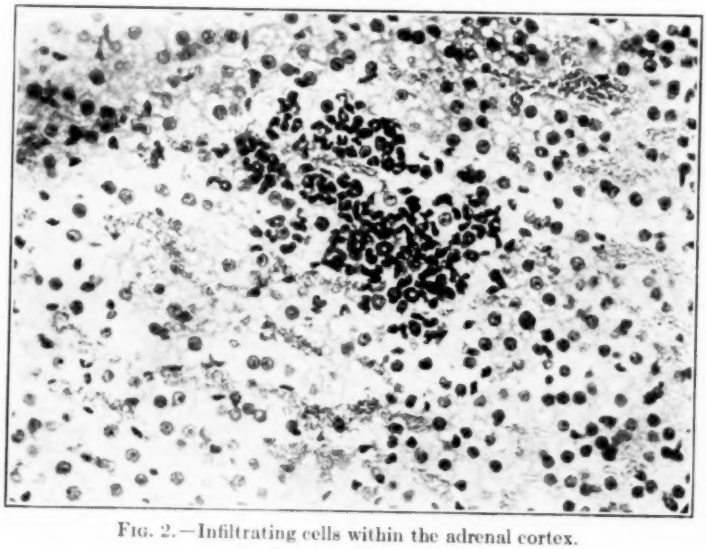

FIG. 2.—Infiltrating cells within the adrenal cortex.

BENCE-JONES PROTEINEMIA IN MULTIPLE MYELOMA.

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Qualitative and quantitative abnormalities of the blood serum proteins have been reported in occasional cases of multiple myeloma. The occurrence of Bence-Jones proteinemia, associated with hyperproteinemia, is, however, so unusual that even a single case is worth recording.

Case Abstract.—T. P., white female, aged 41, was admitted to this hospital, January 8, 1934, service of Dr. McCrae, complaining of severe pains in back, radiating down legs and up left side of body; precordial pain and dyspnea on exertion, that had been present for 3 months. Her previous health had been good.

Physical examination revealed marked pallor, slight enlargement of heart to the left and tenderness over ribs and scapulæ. Pulse, 80 to 120; blood pressure, 140/70; respirations, 22; temperature ranged from 98 to 100° F. during stay in hospital.

Roentgen ray examination: areas of bone destruction in 1st, 6th, 7th and 9th ribs, both clavicles, both scapulæ, skull, both humeri and femurs, pelvis, left ulna and right radius. Diagnosis: multiple myeloma.

Laboratory Studies. *Urine* (January 17, 1934). Sp. gr. 1012 to 1020; cloud of albumin, few granular casts; Bence-Jones protein in large amounts. Several examinations revealed essentially the same findings.

Table 1.—Blood Chemical Findings.

Date.	NPN mg. %	Creat. mg. %	Cholesterol mg. %	Ca mg. %	P mg. %	CO_2 capacity vol. %	Total protein gm. %	Alb. gm. %	Glob. gm. %
1–18–1934	93.3	6.1	147	12.9	5.8	37	8.7	2.9	5.8
1–31–1934	84.5	6.5	...	9.2	6.8	32	11.3	2.8	8.5

Table 2.—Blood Protein Partition.

Date.	Total protein.*	Alb.*	Glob.*	Precipitated protein (80° C.)	
		Grams per 100 cc.		By difference.	Direct determination.
1–18–1934	5.5	2.9	2.6	3.2	3.0
1–31–1934	5.7	2.8	2.9	5.6	5.2

* In supernatant fluid after precipitation at 80° C. and centrifugation.

Blood Count. Hemoglobin 28 to 30% (Dare); red blood cells 1,300,000 to 1,900,000; white blood cells 1700 to 4700; differential count essentially normal.

Wassermann and Kahn reactions negative.

The patient received three whole blood transfusions of 200 cc. each and left the hospital against advice on February 3, 1934. She was subsequently

admitted to the Philadelphia General Hospital (February 18, 1934) where she died.

The diagnosis of multiple myeloma (granulocytic type) was confirmed at *autopsy*, the report of which was made available through the courtesy of Dr. R. P. Custer. The kidneys showed chronic nephrosis with diffuse interstitial fibrosis and the parathyroid glands were slightly enlarged, showing fatty infiltration on histologic examination.

It is of interest to note that a few days before death (February 27, 1934) the blood creatinin had risen to 13.6 mg. and the serum phosphorus to 12.5 mg. per 100 cc.; the serum calcium was 9.2 mg. while the total serum protein had fallen to 6.84 gm. per 100 cc.

Special studies of the serum for Bence-Jones protein were performed as in the cases reported by Wintrobe and Buell[1] and Shirer, Duncan and Haden.[2]

1. The serum was heated in a water bath. Precipitation was observed to begin at 52° C., gradually increasing with an increase in temperature to 65° C. The degree of precipitation was distinctly less at 85°, increased again upon cooling to 65° and disappeared at 10° C.

2. The serum was heated to 80° C. and was centrifuged at high speed for 20 minutes. The supernatant fluid was removed and was examined for total protein, albumin and globulin. These values are presented in Table 2.

3. The precipitate was washed with and suspended in distilled water and the protein content of the suspension determined. The values obtained for the two specimens were 3 and 5.2 gm. per 100 cc. respectively, being slightly lower than the figures obtained by the indirect method cited above.

4. After washing several times with water, a portion of the precipitate was treated with alcohol of increasing strength, then with absolute alcohol followed by ether and finally it was dried in a vacuum desiccator over sulphuric acid. The white powder thus obtained responded to the usual protein color reactions, was readily soluble in dilute acids and alkalies and precipitated from such solutions upon neutralization. Precipitation occurred in the faintly acid solution at 50° C., was apparently complete at 75° C. and the precipitate went into almost complete resolution upon boiling.

Discussion. Attention has been directed in recent years to the occasional occurrence of hyperproteinemia in patients with multiple myeloma. Values for total serum protein ranging from 9.35 to 13.84 gm. per 100 cc. have been reported by Perlzweig, Delrue and Geschickter,[3] Bannick and Greene,[4] Wintrobe and Buell,[1] Shirer, Duncan and Haden,[2] Bönninger,[5] Reimann,[6] Johansen,[7,8] Jores[9] and Kumpf.[10] Qualitative abnormalities of the serum proteins have also been noted by a few observers. Bence-Jones protein or a protein resembling it has been demonstrated in the blood plasma of individuals with multiple myeloma by Ellinger,[11] Askanazy,[12] Jacobson,[13] Abderhalden,[14] Gabbe,[15] Hewitt,[16] Zadek and Lichtenstein,[17] and Shirer, Duncan and Haden.[2] Shirer, Duncan and Haden[2] and Short and Crawford[18] described the formation of a heavy precipitate in the process of inactivating the blood serum at 56° to 60° C. during the performance of the Wassermann test. Wintrobe and Buell[1] observed spontaneous precipitation, at room temperature, of an abnormal protein which, however, did not conform to the recognized characteristics of Bence-Jones protein; furthermore, the latter substance could not be demonstrated in the urine.

The characteristics of the abnormal protein in the blood plasma in the present case correspond closely to those of Bence-Jones protein. It is interesting to note that the substance was precipitated with the globulin fraction (by 22.2% sodium sulphate) in the determination of serum albumin. Similar findings were obtained by Shirer, Duncan and Haden[2] in 2 cases, suggesting the close relationship between Bence-Jones protein and globulin which has been stressed by Hopkins and Savory[19] and Taylor and Miller.[20] The purified preparation gave practically typical precipitation reactions of Bence-Jones protein except for the fact that resolution was not complete at 100° C. This, however, may have been due to the presence of a small quantity of globulin, carried down with the precipitate of Bence-Jones protein.

This combination of hyperproteinemia and Bence-Jones protein in the blood of patients with multiple myeloma has apparently been conclusively demonstrated previously only by Shirer, Duncan and Haden[2] although it probably also existed in the case reported by Jacobson.[13] The frequent failure to detect Bence-Jones protein in the blood is probably due to the fact that its characteristic properties of precipitation at relatively low temperatures and resolution at higher temperatures are by no means invariably exhibited. These phenomena are influenced by several variable factors, including the hydrogen-ion concentration, various electrolytes, organic compounds and the quantity of Bence-Jones protein. Although this substance has been isolated in pure, crystallin form from the urine by Bayne-Jones and Wilson,[21] there is abundant evidence, as stated by Wintrobe and Buell,[1] that it should be regarded not as a chemical individual but rather as a "class of substances which exhibit in common this peculiar precipitation phenomenon." Although the characteristic precipitation at 50° to 60° C. of a protein obtained from blood plasma has been reported by several observers, as noted above, partial or complete resolution at higher temperatures has been reported previously only by Ellinger,[11] Abderhalden[14] and Shirer, Duncan and Haden.[2]

Hypercalcemia has been observed in several patients with multiple myeloma. Serum calcium values ranging from 11 to over 18 mg. per 100 cc. have been reported by Barr and Bulger,[22] Bulger and Gausmann,[23] Jores,[9] Caylor and Nickel,[24] Shirer, Duncan and Haden,[2] Gutman, Swenson and Parsons[25] and Reimann.[6] Of interest in the present case is the fact that the serum calcium concentration of 12.9 mg. per cent fell to 9.2 mg. although the serum protein concentration simultaneously increased from 8.7 to 11.3 gm. per 100 cc. The diminution in serum calcium may have been due in part to the increase in serum inorganic phosphorus but it cannot be satisfactorily explained solely on this basis. One must admit that the hypothesis that hypercalcemia in multiple myeloma is dependent upon hyperproteinemia, although plausible, is far from being well established. The possible existence of a state of secondary

hyperparathyroidism, the excessive mobilization of calcium from involved areas of the skeleton, and the presence of marked renal functional impairment and acidosis are complicating factors of probable importance in this connection. Of particular clinical importance is the fact that both the serum calcium and the serum protein concentrations fluctuated considerably during the period of observation (7 weeks), emphasizing the necessity for repeated studies, particularly when normal findings are obtained.

Summary. 1. A case is reported of multiple myeloma (granulocytic type) with severe anemia and renal failure. Bence-Jones protein was present in the urine and was also demonstrated in the blood serum.

2. The total serum protein concentration varied between 6.84 and 11.3 gm. per 100 cc., the Bence-Jones protein being approximately 3 gm. when the total protein was 8.7 gm. and 5.2 gm. when the latter was 11.3 gm. per 100 cc.

3. Hypercalcemia (12.9 mg. per cent) was present at the time of admission, the serum calcium concentration falling to 9.2 mg. per cent while the serum inorganic phosphorus concentration increased from 5.8 mg. to 12.5 mg. and the blood creatinin from 6.1 mg. to 13.6 mg. per 100 cc.

4. The relatively rapid and marked fluctuations in serum protein and serum calcium concentrations in patients with multiple myeloma and the variability of the several factors which determine the characteristic precipitation reactions of Bence-Jones protein emphasize the necessity for repeated studies in such cases.

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BOOK REVIEWS AND NOTICES

PHYSIOLOGY IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1156, 182 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $9.00.

THIS book is not only a detailed textbook of normal physiology but also deals with functional changes in pathological conditions. We have here a most fortunate opportunity of benefiting by the knowledge of an experimental physiologist who is willing to apply his research experience to clinical matters.

Too often are physiologists unwilling to discuss the functional changes in abnormal conditions in man, sometimes perhaps because the physiologist is a doctor of science and not a doctor of medicine. It therefore often becomes necessary for the pathologist or the clinician to attempt application of his own perhaps hazy arm-chair knowledge of recent developments in physiology to the clinical conditions that confront him. But in this book, Dr. Wiggers makes these applications for him, in such matters as headache, sleep loss, deafness, clinical motor and sensory disturbances, visceral pains, diseases of the blood, clinical disturbances of respiration and circulation and of the gastro-intestinal tract, hypertension, edema of various clinical types, metabolic and endocrine diseases and many other clinical conditions.

This book is a storehouse of critically selected information both for those who are essentially interested in pure physiology and for those who are clinicians and pathologists. I. Z.

HEREDITY AND DISEASE. By OTTO L. MOHR, M.D., Professor of Medicine, The Royal Frederiks University, Oslo. Pp. 253; 107 illustrations. New York: W. W. Norton & Co., Inc., 1934. Price, $3.50.

THIS monograph is the outcome of a series of Dunham lectures delivered at Harvard University during the past year. The author states that his book represents an attempt to arouse interest in the rôle played by hereditary factors in bringing about disease conditions. The Reviewer has no doubt but that Professor Mohr has admirably succeeded in his aim. There are discussed in a clear and readable style such topics as the Mendelian law of heredity, the genes, dominance and recessiveness, the basic concepts of the relation of heredity and disease, the mechanism of set determinations; intermarriage, etc. All of these topics are of interest not only to the physician but to the educated layman as well. The illustrations are for the most part well chosen diagrams. It is hoped that this work may prove an introduction to a field that is of constantly increasing importance to medicine, indeed to every field of biology. B. L.

THE CONSTITUTION AND ITS REACTION IN HEALTH. By T. E. HAMMOND, F.R.C.S., Assistant Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 160. London: H. K. Lewis & Co., Ltd., 1934. Price, 7/6.

MUCH of interest and importance to both layman and clinician is to be found in this attempt to recapture appreciation of the importance of the constitution in health and in convalescence. The Constitution in Disease is to be dealt with in another book. Though the author is aware of modern

studies of the constitution (Draper and Hurst even being quoted with approval), Jonathan Hutchinson is his high priest and Hutchinson's "Pedigree of Disease" his Pentateuch. A characteristically British sanity warns convincingly against excesses of fresh air, sun, bathing and exercise and sagely advises about the differences in the rules of health at different ages and for the hyposthenic and hypersthenic types. Though there is too much deduction from analogy and few would accept today such opinions as that the full moon has an effect upon those with mental disorders, or that mercury and gold act beneficently on the centers of energy, nevertheless the book as a whole emphasizes forcibly a point of view that today sadly needs forcible emphasis. E. K.

TUMORS OF THE FEMALE PELVIC ORGANS. By JOE VINCENT MEIGS, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Surgeon to Out-patients, Massachusetts General Hospital, etc.; with a foreword by ROBERT B. GREENOUGH, M.D., President-elect of the American College of Surgeons, 1933–34; etc. Pp. 533; 261 illustrations, some in colors, and 49 tables. New York: The Macmillan Company, 1934. Price, $6.00.

IN this thorough exposition of the new growths of the female pelvis, Dr. Greenough states that no other group of tumors has created so much interest in their relation to the glands of internal secretion, and no other group has benefited as much by the use of radiation. A discussion of etiology, diagnosis, pathology and treatment—based upon a wide clinical experience—precedes a full pathologic and follow-up study of a fair sized group of cases from the Massachusetts General Hospital, and a discriminative sifting of the literature upon the subject. The clinical teaching is eminently sound, the pathology is copiously illustrated by many color plates and photographs and well executed photomicrographs. The literary references are carefully chosen and as well digested in the text.

Of particular interest is the section on rare tumors of the ovary, the malignant embryonal types, disgerminomas and arrhenoblastomas. The section on cancer of the cervix uteri is most complete. The section on treatment and follow-up deductions based upon tumor type is excellent.

The use of the classification of the American College of Surgeons affords a comparable value for the results shown. This is a triple offering for the use of the gynecologist or surgeon, the pathologist and the roentgenologist and should be of much practical service to any of the three groups.

P. W.

THE HEART VISIBLE. A CLINICAL STUDY IN CARDIOVASCULAR ROENTGENOLOGY IN HEALTH AND DISEASE. By J. POLEVSKI, M.D., Attending Physician and Cardiologist, Newark Beth Israel Hospital. Pp. 207; 122 illustrations. Philadelphia: F. A. Davis Company, 1934. Price, $5.00.

THE author states that this book is for the radiologist who has the scientific curiosity of a clinician and for practitioners who do not realize the value of a roentgen examination in cardiovascular conditions. Though he states that most of the films and tracings have been verified at autopsy, throughout the book he neglects to indicate which cases are so confirmed. Some of his conclusions do not agree with my impressions but the lack of autopsy confirmation leaves one unable to determine whether the author was correct in his premises. Under "General Considerations and Methods of Roentgenologic Studies," the author has left out a considerable amount of information that the radiologist who is unfamiliar with this subject

would desire. It should be said, however, that if one reads carefully through the entire book, most of the things that I have reference to are either mentioned in the text or shown in the illustrations. The use of barium studies is not adequately explained; the use of various postures in demonstrating cardiac lesions is not touched upon; the use of the Bucky diaphragm is excluded. Mediastinal and vertebral lesions are not considered. Possibly the Reviewer is a little too critical in this comment, but many of these procedures have long been a valuable routine among radiologists in large institutions. The author, in discussing fluoroscopy, does not emphasize the necessity for well accommodated eyes, especially in the demonstration of sclerosis of the coronary vessels or calcification of the valves. The author then considers the normal heart, abnormal heart, pericardium and great vessels. There is an extensive bibliography after each chapter, but nowhere is it referred to in giving credit to the original authors. One is struck with the great predominance of foreign authors in the bibliography even though well-known American authors have noticeably escaped the author's attention. The chapter devoted to congenital heart lesions is relatively small. Under the great vessels the author did not include the rather important subject of dissecting aneurysm. The illustrations, diagrams and print used in this book for the most part are excellent. It should find a certain demand, but the radiologist who looks to have the subject of cardiac radiologist thoroughly covered will be disappointed. E. P.

BENIGN ENCAPSULATED TUMORS IN THE LATERAL VENTRICLES OF THE BRAIN. Diagnosis and Treatment. By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, Johns Hopkins University. Pp. 189; 83 illustrations, 2 tables. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.50.

DANDY reports on 40 benign encapsulated tumors in the lateral ventricles, 15 of which are his own personal cases, and 25 are collected from the literature. In addition he mentions briefly 7 small tumors of the choroid plexus and a small group of malignant tumors of the lateral ventricles.

He concludes that there is no syndrome characterizing the benign ventricular tumors and expresses "a very serious doubt that a clinical syndrome for tumors in the lateral ventricles can ever be established." In the last analysis the diagnosis depends on ventriculography which accurately locates the tumor and provides the surgeon with important information concerning the approach to the tumor by operation. In Dandy's 15 cases, localization was made by ventriculography in 11, by ventricular estimation in 2, by neurologic signs in 1 and by a misdirected cerebellar operation in 1. The changes produced in the ventricular system by tumors in the lateral ventricles are: (1) A border or filling defect of the tumor; (2) hydrocephalus; (3) deformity and dislocation of the ventricular system. Dandy says, "Absolute precision in localization of the tumor by ventriculography must dictate the exact site of the operative exposure. A misplaced exposure is certain to be productive of extensive injury to the brain and will probably end in a fatality."

The operative mortality in Dandy's series was 20% with no deaths in the last 7 cases and no recurrence in the last 12 cases. The longest survival is 15 years, the next 13 years. Dandy thinks recurrence will be unlikely.

The pathology of these tumors is varied. Four arose in the glomus of the choroid plexus; 1 was an angioma, 1 an adenoma and 3 others are classified as "pure fibromata of the choroid plexus." The other tumors were not easily classified, being different from all other intracranial tumors excepting some arising from the third ventricle. They are encapsulated

and often attached to the ependyma. Their encapsulation and failure to recur led him to classify them as benign. Their histologic features are more or less disregarded from this standpoint.

The illustrations are clear and convey a good deal of valuable meaning, but the case reports are poorly constructed. Articles are frequently omitted and the style of the case reports recalls too vividly many cryptic hospital case records. The pathologic study of the specimens leaves a great deal to be desired, but as Dandy himself says, he must "defer the ultimate microscopic classification to more competent students of pathology." The tumors represent an interesting group but the report might easily have been included in a single article rather than a monograph.

B. A.

DIÄTTHERAPIE DER LUNGENTUBERKULOSE. By DR. MAX GERSON, Wien, Mit Röntgenbefunden und einem Röntgenkapitel von DOZENT DR. FELIX FLEISCHNER, Wien. Pp. 619; 154 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 36.

IN this comprehensive work the author presents the principles, practical application and clinical results of his dietary therapy for pulmonary and other forms of tuberculosis, which is known as the Gerson diet, and describes those difficulties and complications which necessitate modifications of the diet in particular conditions. Emphasis is placed on favorable results in severe and very severe cases which had either failed to benefit by previous surgical procedures or in whom such procedures were impracticable.

The author has treated about 650 cases of pulmonary tuberculosis with the Gerson diet during the past 11 years, most of which were ambulatory patients. In 1932 Prof. Zondek placed for 1 year 25 pulmonary cases of the Urban Hospital, Berlin, under the author's direction. These cases were selected by Freund and Zondek as patients regarded as therapeutically uninfluenceable, but the study was interrupted by the National Socialist Revolution.

No accessory therapies of any kind were employed. The medication consisted of administration of phosphorized cod-liver oil, Gerson's mineral mixture, calcium bromid, caffein enemas, and a few patients received, in addition, hormonal preparations (vigantol, codein and coagulen) occasionally. Twenty-six private cases are also described in great detail.

The blood chemistry was followed in all cases and roentgenograms were taken at regular intervals of 3 to 7 weeks, all of which were interpreted by Fleischner of Vienna. In a chapter on "The Anatomic and Roentgenologic Morphology of the Curative Processes in Pulmonary Tuberculosis," atelectasis receives special consideration.

No less than 29 chapters are devoted to theoretical and practical considerations relating to predisposition, immunity, anaphylaxis, allergic diseases associated with tuberculosis, exacerbations, dietary therapy as an antiallergic treatment, tuberculous inflammation and the tissue reaction and edema, acid and alkaline therapy, demineralization and transmineralization, the mineral metabolism, etc.

The theoretical part is followed by full details of the practical application of the Gerson diet, the medication, accessory therapies, etc. Here it may be well to point out that the author has repeatedly modified the Gerson diet since its first introduction in 1923 and that he claims for the latest modification, which dates from 1932, better and quicker results than for the previous forms of this dietary.

The application of the present Gerson diet with its four phases and numerous substages is very laborious and complicated; it behooves us therefore to inquire whether the results which this therapy is capable of

yielding justify these efforts. The author points out that the results mainly based on 51 cases of pulmonary tuberculosis with cavitation were obtained under climatically unfavorable conditions in cities, and that a more favorable environment would probably yield even better results because altitude, isolation, etc., would tend to support the dietary therapy.

Of the 51 cases, 5 (10%) were mild ones, 5 (10%) moderately severe, 23 (45%) severe, and 18 (35%) very severe. The 41 severe cases involved tissue destruction of so far-reaching a nature that the literature contains only a few references to similarly favorable results in such cases. Particularly 8 of the 18 very severe cases showed results which the author regards as of fundamental importance because they illustrate possibilities in the cure of tuberculous lung tissue which have so far been underestimated by anatomists.

On the basis of his entire experience the author claims that the Gerson diet is capable of curing the most severe forms of pulmonary tuberculosis and that even cases which have hitherto been regarded as hopeless can be saved by it. On the other hand, the diet must not be regarded as a prophylactic against renewed infection unless it is followed by adequately prolonged suitable dietary after-treatment. The author states that the dietary treatment, if carried out as directed, must necessarily show the patient's improvement (influence on cavities) in the roentgenograms, though the time in which this manifests itself will vary greatly.

The claims advanced by the author are not in line with the results obtained by the majority of the clinicians who applied the older forms of the Gerson diet in pulmonary tuberculosis. Nevertheless, having regard for the modification of the diet and the impressive material which is now presented, this book should prove of interest to clinicians, and suggests the desirability of further study of the diet. Comprehensive authors' and subject indexes and numerous references to the literature are given.

E. M.

FRANKLIN PAINE MALL, ANATOMIST. By FLORENCE RENA SABIN. Pp. 342; 6 illustrations. Baltimore: The Johns Hopkins Press, 1934. Price, $2.75.

THE author, who worked for 20 years under Mall at Baltimore, having prepared for the National Academy of Science an analysis of his scientific activities, has now, at Dr. Welch's suggestion, prepared Mall's biography, a companion volume to McCallum's *Halsted*. After an unpromising start in our Mid-West, she tells us how he was fortunate enough to go to Germany for postgraduate study in "the golden age of the German University." First studying ophthalmology at Heidelberg, he moved on to anatomy and embryology with His and especially to physiology with Carl Ludwig, from which two men he caught the inspiration that he so richly passed on to others. There he became steeped in a thoroughly congenial scholarly atmosphere that bore its important fruit, when, in 1893, he was invited to organize the department of anatomy at the new Hopkins Medical School. His teaching was to be of the elbow, inductive variety (only partly because he was a poor lecturer) and the teacher, even in his students' routine dissections had always to be the investigator. He did not regard his reforms in the teaching of anatomy as "Germanizing the dissecting room," but rather as "dependent more on what Huxley did and said." (Letter to Arthur Keith.) "Your body is your own text book" is excellent self education for the good students, but one might interpolate that his attitude toward the poor ones (like his remark to his wife as he watched her bathe her baby, "Why don't you just throw her in and let her work out her own technique?") could hardly produce satisfactory results, nor

did he expect it to or seem to care. Severely critical and caustic at times, yet amusing and kindly at others, this complex personality has been deftly handled by Dr. Sabin. As his "character of teaching" she takes L. C. Miall's assertion: "The spirit of enquiry is only to be communicated by those who habitually enquire themselves." The story is interesting and authoritative—the mistakes few: As far as I know, Shippen never spelled his name with an "a" and it is surprising to see him linked with Leidy as a contemporary. This story of a great investigator's development should be of special interest to medical readers as it coincides with the most important change in medical education that this country has experienced in more than a century. E. K.

THE BRAIN AS AN ORGAN. Its Postmortem Study and Interpretation. By FREDERIC WERTHAM, M.D., Formerly Associate in Psychiatry, Johns Hopkins Hospital and Medical School, etc., and FLORENCE WERTHAM, Formerly Charlton Fellow in Medicine, Johns Hopkins University, etc. With an Introduction by ADOLF MEYER, M.D., Psychiatrist-in-Chief, Johns Hopkins Hospital. Pp. 538; with text illustrations and 166 plates. New York: The Macmillan Company, 1934. Price, $7.50.

THE several texts on neuropathology that have appeared during the past two years indicate a revival of interest in the structural pathology of the nervous system. The present book is a valuable addition. As the title suggests, this work is an attempt to integrate neuropathology, to consider the brain as an organ rather than as a composite of many more or less independent loci of nervous activity. This point of view is presented in a stimulating introductory chapter from which the following may be quoted: "It is not exaggeration to describe current practice by saying that general pathologists study the human organism as a body without a brain, while neurohistologists study the brain as an entity without a body. General pathologists have been inclined to regard the brain as any organ so far as technical methods are concerned, but as something totally different in respect to the interpretation of lesions. Just the opposite should be done. The dissociation of neuropathology from general pathology was perhaps inevitable until it had formulated its own problems and worked out its own methods. The next step, in our opinion, must be a closer union with general pathology."

This indeed is as it should be. Several chapters are devoted to the technique of macroscopic and microscopic examinations of the brain, and to discussion of the kinds of lesions of the nervous parenchyma and their distribution. B. L.

NEW BOOKS.

Diabetes Mellitus and Obesity. By GARFIELD G. DUNCAN, M.D., C.M. (McG.), Associate in Medicine in the Jefferson Medical College, Philadelphia; Assistant Physician to the Pennsylvania Hospital, etc. With an Introduction by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, etc. Pp. 215; 9 illustrations and 40 tables. Philadelphia: Lea & Febiger, 1935. Price, $2.75.

Stammering and Allied Disorders. By C. S. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (ENG.). Pp. 182. New York: The Macmillan Company, 1935. Price, $2.00.

A Summary of the Treatment of Fractures and Dislocations. By R. Broomhead, M.B. (Leeds), F.R.C.S., Surgeon, Orthopedic Department, General Infirmary at Leeds; Consulting Orthopedic Surgeon, St. James's Hospital, Leeds, etc. Pp. 39, mostly tables. Leeds: Jowett & Sowry, Ltd. (Printer). Price, 3/6 including postage, from Mr. Henry Walker, Briggate, Leeds.

Poliomyelitis. A Handbook for Physicians and Medical Students. By John F. Landon, M.D., Attending Physician, Willard Parker Hospital; Special Consultant in Pediatrics, Woman's Hospital, New York, etc., and Lawrence W. Smith, M.D., Pathologist, Willard Parker Hospital, etc. With a Section on the orthopedic after care of the disease by Garry DeN. Hough, Jr., M.D., F.A.C.S., F.A.A.O.S., Attending Orthopedic Surgeon, Shriners' Hospital for Crippled Children, Springfield, Mass. Pp. 275; 18 illustrations. New York: The Macmillan Company, 1934. Price, $3.00.

The Clinical Aspects of Visceral Neurology. With Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. Livingston, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Pp. 254; 46 illustrations. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

The Technique of Post Mortem Examination. As Practised in the Pathological Institute of McGill University at the Royal Victoria Hospital, Montreal. Compiled by D. R. Coman, M.D., C.M., Assistant to the Instructor and Demonstrator in Pathological Anatomy. Pp. 47; 12 illustrations. Montreal: Renouf Publishing Company, 1934. Price, $1.40.

Medical Tactics and Logistics. By Colonel Gustavus M. Blech, Medical Reserve Corps, U. S. Army, and Colonel Charles Lynch, Medical Corps, U. S. Army, Retired. Pp. 205. Springfield, Ill.: Charles C Thomas, 1934. Price, $4.00.

Report on Seventh International Congress of Military Medicine and Pharmacy, Madrid, Spain, May–June, 1933. By William Seaman Bainbridge, Captain, M.C.–F., United States Naval Reserve; Member of the Permanent Committee, Delegate from the United States. Pp. 88; illustrated. Menasha, Wis.: George Banta Publishing Company, n.d. (Price not given.)

An interesting report covering medical services in wartime, military vaccination, preserved foods, dental, veterinary and similar topics. E. K.

One Hundred and Fifty Years of Publishing, 1785–1935. [Henry Charles Lea]. Pp. 42; illustrated. Philadelphia: Lea & Febiger, 1935.

Die Werke des Hippokrates. Herausgegeben von Dr. med. Richard Kapferer unter Mitwirkung von Prof. Georg Sticker, Würzburg. Part 3: Die Diät (Lebensordnung) 1. und 2. Buch (Price, Rm. 2.50); Part 4: Die Diät (Lebensordnung) 3. Buch. Die Träume / Die gesunde Lebensordnung (Price, Rm. 2.10). Pp. Part 3, 96; Part 4, 80. Stuttgart: Hippokrates-Verlag G.M.B.H., 1934. (To be published in 25 parts costing ca Rm. 100, card binding.)

The Medical Clinics of North America, Volume 18, No. 3 (New York Number, November, 1934). Pp. 301; 17 illustrations. Philadelphia: W. B. Saunders Company, 1934. Price, per clinic year July, 1934, to May, 1935, Paper, $12.00, Cloth, $16.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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STUDIES ON STAPHYLOCOCCI.

CONSIDERABLE progress has been made recently in our understanding of the pyogenic cocci and the many types of infection they produce. Last year studies on hemolytic streptococci were considered and this year we are giving a similar discussion of the staphylococci. Staphylotoxin has more or less dominated the investigations in the last few years, but many phases of the problem of staphylococcal infection have been stimulated and better methods for classification and biologic studies have been developed.

Differentiation. *Pigment.* The recognition of the pathogenic and virulent strains of staphylococcus has always been difficult, since no fully satisfactory criteria for the purpose have been at hand. Thompson has attempted a division into three groups, chiefly on morphologic differences but, although this may help to eliminate certain larger forms which are of little significance in infection, it can be of little help to the larger problem. Although the aureus strains have long been considered as of exclusive importance, this view cannot be held too rigidly today. It is well recognized that several of the strains used by investigators for the production of toxin give white colonies (Nélis *et al.*) or white substrains (Bigger). Burnet used a white variant as the standard toxicogenic strain, and Parish, O'Meara and Clark found the lightly colored aureus better than the deeply colored parent strains.

Pinner and Voldrich reported the derivation of Staphylococcus albus, citreus and roseus from pathogenic cultures of Staphylococcus aureus. The albus strains could be changed back to aureus strains by long growth in the presence of antialbus serum. These derived strains were all apathogenic strains. These authors believe "it may be wise not to dismiss too lightly the finding of Staphylococcus albus in human tissue or body fluids" and the Reviewer agrees that the evidence from toxin and other products of staphylococci sustains this view. Hoffstadt and Youmans further describe the dissociation of a virulent Staphylococcus aureus into a number of colony forms with or without color changes and differences in speed of fermentation and substances fermented, with loss in all of the virulent feature of the original, but

with antigenic specificity by the agglutination and complement-fixation tests. They suggest that mixtures of these forms in cultures may account for the irregular findings in fermentation and other tests and that the avirulent form may remain in the body and, when virulence returns, produce lesions. In a more recent article these writers have discussed the genetic significance of such dissociants. Panton, Valentine and Dix have shown that the pigment, resembling carotin, has by itself no local or general effect in rabbits and that humans, sensitive or not to staphylococci, gave no reaction to it. Goadby found the removal of the lipoid material by alcohol and ether did not affect the antigenic power of the staphylococci to produce agglutinins but benzoylation prevents agglutinin production for the intact cocci. It will be generally agreed that the pigment responsible for the aureus color is not the determining factor in the infectivity of staphylococci, but the high incidence of Staphylococcus aureus in human and animal infections must not be lost sight of in the search for useful criteria of pathogenic strains. Most investigators have noted the frequent correlation of pigment with other characters of significance in infections. Chapman *et al.*, after a study of some 5000 strains, have stressed the importance of an accurate determination of the color production in recognizing the toxic types of staphylococci along with hemolysis and coagulase activities.

Cultural Methods. Hughes studied the growth requirements of Staphylococcus aureus and separated an activating substance from meat extract, belonging to the chemical group of "natural bases" which was heat stable in slightly acid or neutral solutions but rapidly destroyed in alkalin solution, was dialyzable through collodion membrane and, when added in an amount less than 1 mg. to 50 liters of synthetic media, activated the latter and gave a good growth of staphylococci. Such a medium should serve as a valuable means for more careful analyses of many of the biochemical activities of these cocci. Birch-Hirschfeld used the culture method of Jacobsthal in which a layer of cellophane covers a thick agar plate. The easily dialyzable substances pass through the cellophane and serve as the medium for the staphylococcus and on which it produces hemolysin, protease and other substances in about 24 hours in larger amounts than on ordinary media. Autolysis occurs in a few days and it is recommended for obtaining autolysates of staphylococci. Clifton noted that cultures of Staphylococcus aureus in broth develop and maintain rather intense reducing conditions. Following lysis by bacteriophage the potential increases to a more positive value. He gives data which suggest that the observed oxidation-reduction potentials are a resultant of the metabolic activity of the cells. A great deal has been learned about the cultural conditions which favor the production of toxic substances. Bigger demonstrated that the reaction during growth is of fundamental importance and showed that the various methods—the presence of phosphate buffer, of carbohydrates or of both, or culture in an atmosphere containing added CO_2—all depend on their buffer action in preventing too great an alkalinity. However, he found that for some strains the carbohydrate (glycerol) method with buffer is superior and with others, the CO_2 method, and further that there are strains for which CO_2 is definitely prejudicial. (See also Nélis *et al.*, Burnet and many recent investigators.) It is clearly evident that many *in vitro* conditions alter and determine the metabolic activity of staphylococci and how these can be correlated with those liable to occur *in vivo* is a matter for

much speculation. Reduced oxygen tension is often present in injured tissues, buffers and carbohydrates are available in varying degrees but there is no certainty as to just what the conditions may be in the great variety of infections by staphylococci.

Modes of Infection. There have been a number of interesting observations relating to modes of infection. Duran-Reynals describes a soluble factor from invasive strains of staphylococci, after autolysis or extraction, which markedly increases the permeability of tissues and enhances the infections produced by these organisms. This factor was studied on 53 strains of staphylococci from human lesions and was found to be closely correlated with aureus characters, hemolytic power and liquefaction of gelatin. Variants toward the albus type were noted in old cultures; the typical R forms, showing cultural changes, were no longer invasive and had no spreading factor but sometimes a white variant retained a number of other characters as well as the invasive and spreading power. He further showed that the spreading factor enters the blood from the local site and increases the permeability of at least the skin and thus may enhance infections by the same or other bacteria in other regions. It differs from aggressin in being non-specific, thermostable and non-antigenic. The tentative inference drawn from his experiments is that virulence and invasiveness are not the same thing. In a later article he discusses the influence of testicle extracts which contains a similar spreading factor and shows that lesions produced by invasive strains of staphylococci in high dilutions or by non-invasive strains at moderate dilutions are definitely lessened in severity or even suppressed by this factor. These studies serve to explain what may happen in certain types of staphylococcus infection. Menkin[1] demonstrated that the trypan blue injected into an area of cutaneous inflammation induced by Staphylococcus aureus, 1 hour after the introduction of the cocci, failed to spread to the tributary lymphatics, while this blockage did not occur with pneumococcus Type I until after 6 or more hours nor with Streptococcus hemolyticus until 30 or 45 hours. This difference is explained by the early production of a fibrin network or thrombosis of the lymphatics by the former organism. A further study[2] of these phenomena showed that filtrates of Staphylococcus aureus fixes trypan blue in the skin of rabbits by causing occlusion of lymphatics and coagulation of interstitial plasma but after heating to 58° C. for 1½ hours does not do so. This filtrate unheated causes swelling, vacuolation and often degeneration of leukocytes suggesting its similarity or identity to leukocidin. The fixation, therefore, seems to be referable to the irritating property of the organism *per se* and also to the damaging effect of this toxin-like product. Sullivan, Neckermann and Cannon studied the localization and fate of staphylococci after intravenous injection in rabbits, finding a rapid removal from the blood, particularly in the liver and spleen and an ingestion and destruction by the phagocytes. The primary localization occurs in organs with many macrophages and a sinusoid type of blood flow, whereas practically none occurs where the macrophages are few and where the blood flow is rapid in vessels with ordinary endothelium. Active intravenous immunization has little or no effect on the comparative localization but leads to a more rapid removal and death of the bacteria due to the stimulation of mesenchymal tissue with an elevation of the functional state of the macrophages. (See a later discussion on the effect of bacteriophage.)

Antigenic Toxic Factors (Staphylocoagulase.) Filtrates of staphylococci have received the major attention of investigators during the last few years and the antigenic toxic factors have been very fully studied. Staphylocoagulase and its action on oxalated or citrated plasma, a characteristic product only of staphylococci, was for a long time thought to require the presence of living cocci for its manifestation *in vitro*, but Gross found it present in filtrates but only of certain strains. He reported it as the first character to appear in cultures; it is heat stable, resisting 70° to 80° C., it disappears from old cultures and he considered it different from the true toxin of staphylococcus. Van Breuseghem used for its study collodion tubes filled with oxalated plasma which were immersed in tubes of the same medium. After seeding the inner tube he noted complete coagulation in 1 or 2 hours followed by a fibrinolysis complete by the next day. The uninoculated exterior plasma is never coagulated, showing coagulase is not dialyzable. Oxalated plasma by itself changes at 37° C., due to alkalin changes, so that it becomes non-coagulable by calcium, but at first it is still coagulated by thrombin, but the plasma in the outer tube is protected by the dialyzable acid from the staphylococcus growth in the inner tube. The plasma thus altered in coagulability is, when seeded with staphylococci, coagulated but not fibrinolyzed. Gengou has studied this phenomenon particularly and has determined that it does not need the presence of the constituents of thrombin. He gave evidence that the responsible substance for coagulation and fibrinolysis of oxalated plasma is a fibrinolytic agent secreted by the bacteria even in media free from fibrinogen such as broth; that it acts on pure fibrinogen but the stage of clotting is very short; and that in the plasma the prolongation of the clotting stage is due to the marked antilytic action of albumin and the lesser action of globulin. Finding the agent to be completely or largely retained by filters, he made use of its resistance to heat to obtain bacteria-free preparations after nearly all the cocci had been previously removed by centrifuging. The agent is resistant to age and desiccation, is heat stable (60° C. for 30 minutes), does not dialyze and is practically retained by filters. Gross[2] showed that only staphylococci among pathogenic germs have this power, and it is so markedly characteristic of Staphylococcus aureus that it serves as a useful test for dividing the pathogenic from the non-pathogenic strains. Chapman *et al.* found coagulase of great value along with hemolysin and color development for the same purpose. Gross found it to be highly resistant to heat—1 hour at 90° C. and in a few even at 100° C. only weakening it. He obtained clotting by injecting it into the veins of animals and suggests the importance in human thrombosis of this germ-free product of these bacteria. He noted that the clotting times of the citrated bloods of different animals varied widely, rabbit blood taking 1 to 2 hours, while other animal bloods take as long as 24 hours. The variation in human blood of from 1 to 2 hours to no clotting at all suggested an antibody which he thought might play a rôle in preventing thrombosis. The presence of this antibody in sera with a high antitoxic content and its development in rabbits after prolonged treatment with filtrates containing coagulase supported his contention. Sudhues and Schimrigh searched for the presence of an antistaphylocoagulase in the plasmas of normal persons and in those with staphylococcus infection of many grades of severity as well as in the plasmas of experimentally infected animals. They were unable to find any deviation

from the average of the normal clotting time of citrated plasma by the staphylococcus in any of these, not even in cases in which antistaphylolysin was demonstrably present, and suggest that the differences are due to some chemicophysical change in the blood and not due to any coagulase inhibiting antibody. Dolman[3] was also unable to demonstrate this *in vitro* inhibition by antitoxic serum.

Hemolysin. According to Gross, hemolysin and leukocidin appear later in cultures than coagulase. Hemolysin does not act the same on the red blood cells of different species. He reported that rabbit blood was most sensitive, bovine less, sheep and goat much less and human, equinine and guinea pig blood gave no hemolysis. Dolman[1] found almost the same order of susceptibility, the hemolytic units for a certain toxin being as follows: Rabbit, 8000; sheep, 1600; cow, 200; guinea pig, 40; human, 20; cat, 10; horse, 10. It has been generally agreed that the rabbit is the most sensitive animal for the study of all these toxic substances, and tests against rabbit red cells are useful for titrating the toxic preparations (Gross[3] and many others). It is, of course, clear that the effects of toxins of staphylococci in humans cannot be interpreted, directly, as due to hemolysin when the toxins have such low titers against human erythrocytes. Sheep cells, as Dolman says, may be hemolyzed by a toxin which gives no necrosis in the rabbit skin. It would appear from these and many similar reported findings that only in the rabbit can correlated results from the different properties of these filtrates be relied upon. Although the majority of workers believe hemolysin is but one manifestation of a common toxin all do not agree. Gross found hemolysin and leukocidin appeared at the same time in cultures. Panton and Valentine, in a study of 22 strains, concluded that hemolysin and the lethal and necrotic action vary closely together but with no relation to the leukocidin. The strains from acute severe infections usually develop strong leukocidin and weak hemolysin and just the reverse occurs in strains from long-standing sycotic types of infection. In an annotation in the *Lancet* (**2**, 261, 1934), covering a criticism of Dolman's[3] reports on the results of serum treatment, it is pointed out that an antiserum should be tested for its power to neutralize leukocidin, for the above reasons. Weld and Gunther, on the other hand, being able to absorb $\frac{9}{10}$ of the hemolysin and leukocidin of their filtrate on red cells or to completely remove leukocidin by leukocytes, leaving the necrotoxin undiminished, concluded the two were different. Burnet and Freeman state that all the work of their laboratories since 1928 leads to the view that all the manifestations of the toxin produced from their standard toxicogenic strain (white staphylococcus variant 86) on the cells and tissues of rabbits are due to a single toxin. They suggest that the previous workers may have had a toxin with an altered toxophore group, like a preparation of a slowly formaldehyde detoxicated "intermediate" toxin of theirs, with antigenic identity but similar differences in the hemolytic and necrotic tests. Burky[1] reported that the invasive, virulent and pathogenic properties are independent of hemolytic and pigment-producing properties and showed that under anaërobic conditions pigment and hemolysin are practically zero without any impairment of the lethal effect, and in a synthetic medium the production of hemolysin is inhibited with no corresponding loss in the lethal factor. Further, his strain (Ha) at first produced moderate amounts of hemolysin and lethal factor, but on later subcultures the hemolysin was lost and

the lethal factor increased and he even suggests that hemolytic activity inhibits the action of the lethal factor. The hemolysin he found to be unstable, while the lethal factor maintains its toxicity for as long as 1 year without refrigeration. Nélis *et al.* state that the rule, the more lysin the more toxin, is not strictly true. He showed that his medium inhibits the action of hemolysin in the more concentrated doses of the filtrate but the hemolysin is attached to the red cells which lyse immediately on removal from the medium. From such evidence as the above it is clear that titration for the hemolysin content of a filtrate may not be correlated with other properties. Chapman *et al.* include hemolytic tests, using rabbit blood agar, as a valuable measure for the identification of pathogenic staphylococci, but they emphasize that coagulase and pigment production also must be determined to make possible a high degree of precision. Antihemolysin is widely used as an index of antitoxic content of artificially and naturally produced antiserums (Gross,[1] and Connor and McKie[1]). Certainly with many of the strains of staphylococcus used for inducing immunity in man and animals it serves as a valuable procedure; but realizing the relatively inert action of the hemolysins produced *in vitro* for human red cells, one wonders whether the artificial antibody content so determined actually indicates a real immunity in the treated human being. Dolman[3] considers the antihemolytic power of antiserum for human therapy as probably of secondary importance from the clinical standpoint.

Leukocidin. This product of staphylococcus growth has been incidentally discussed above, but because the purulent character of staphylococcal infections provides a sharp differentiation from many other infections by known toxin producers, such as in diphtheria and tetanus, it should be considered of prime importance in the study of staphylococcus infections. Most investigators have stressed its significance but, largely for technical reasons, it has not recently been systematically studied although such a study is full of promise. Menkin[2] thought a leukocidin-like substance might be responsible for the irritating effect determining localization by fibrin deposition in the lymphatics, although the Reviewer would suggest the probability that the factor is more of the nature of staphylocoagulase, although the latter is heat stable. Panton and Valentine consider leukocidin as different from both hemolysin and the necrotoxin. The fact that antitoxic immunity rarely protects against the living bacteria in experimental animals and from the evidence of high antitoxin content in infected patients (antihemolysin), presumably also in man, this opens up the problem of a more basic explanation for the purulent character of these infections. Although phagocytosis is almost universally accepted as the chief fundamental defense against these cocci, the idea has been advanced that the proteolytic action of an excess number of leukocytes may be a contributory or even a prime factor in the development of the purulent lesions. There is a possibility that materials from the leukocytes may be absorbed by the peripheral nerves and interfere with the normal reflex control of the infected tissue. Benians discusses the problem of pus in infection. If a patient survives the first few days of a pyemia, he emphasizes, the outlook is related to the condition of pus formation rather than to the actual toxic virulence of the infecting agent. He quotes Wright as saying that normal blood contains phagocytes "far in excess of any conceivable requirements." In a series of 4 cases of severe osteomyeli-

tis he gave benzol by mouth to reduce the leukocytosis with good results and based this treatment on the following: Patients quite often die from the violence of their reactions rather than from the virulence of the infections; it seemed as logical to attempt to check hyperleukocytosis as to check hyperpyrexia; leukocytosis increases as immunity develops, and with the neutralization of the toxins the pyogenic capacity of an infecting organism is apt to increase; leukopenia is the result of toxin alone; and he believed leukocytosis and localization of pus is an index rather than a necessary adjunct of immunity. He hopes that a more direct method may be discovered for this purpose. The Fs type of Staphylococcus aureus described by Burky,[1] with low toxicity and marked pyogenic characters, supports Benians' hypothesis as does also Gross,[4] who found his less toxic strains were derived from osteomyelitis cases. Schattenberg and Harris studied the effect upon animal leukocytes of a Staphylococcus aureus culture from a case of "agranulocytic angina." Suspensions injected into the subcutaneous tissue, the peritoneum, the peritonsillar structures, on and in the scarified tracheal mucosa and into subcutaneous agar, caused neutrophilic leukocytosis or no cell reduction. Filtrates acted similarly. However, the exudate following intraperitoneal injections of guinea pigs, when filtered and injected intracardially and intraperitoneally into animals, produced a granulocytopenia. Pike described a phagocytic depressing effect of filtrates of staphylococci quite independent of their hemolysin or toxic characters. The depression effect is not antigenic, is thermostable, does not deteriorate on standing (4 weeks), is unaffected by an atmosphere of CO_2 and, a similar substance being formed by Escherichia coli, it is not specific for staphylococcus. He concluded from this and the early report of Van de Velde, in 1894, that leukocidin is not the cause of virulence.

Necrotoxin. The presence of this substance in a filtrate is discovered by its power to produce necrosis in the skin of rabbits. Gross found it appeared only in older cultures (later than hemolysin and leukocidin) along with the lethal toxin and showed it can be preserved in the dry state. In its lability to heat it resembles hemolysin. The test for necrotoxin is not easy to standardize. Dolman[1] used as the criterion an edematous white or yellow patch on the second or third day with a rim of erythema, but if a scab or necrosis is demanded then the titer is much lower. Nélis *et al.* required a scar. Gross[4] divided his strains into three groups by the type of reaction as giving (1) necrosis, (2) red infiltration and (3) negative reactions. Burky[2] particularly showed how important the breed of rabbit was for the type of skin reaction and described similar kinds of reactions with his three types of organisms and indicated that the sensitivity to the barium sulphid depilatory foretold what the reaction would be to filtrates. Another source of confusion is the marked differences in the "normal" antitoxin in rabbits and this should always be tested as antinecrotic rather than antihemolytic (which is rarely done) before the animal is used for the test. Burky[3] further showed that age was of great significance in that young rabbits under 4 months were non-reactive to the cutaneous injection nor can they be killed even by large intravenous injection. This is not due to an immunity but suggests to him that the reaction is of an allergic type. Kobak and Pilot had previously noted the same phenomenon in humans, using vaccines and filtrates, finding that newborn babies failed to react when the mothers did and that this

reactivity gradually developed with age. Dolman[1] found older guinea pigs were relatively more susceptible to the lethal effects of filtrates than were younger ones. Connor and McKie[1] suggest that the antitoxin effects after toxoid treatment may be due to desensitization. Panton, Valentine and Dix induced immunity by intradermal injection of staphylococci and found antibodies present in his animals in that a smaller lesion followed an injection, but there was also an increased sensitivity in that lesions were produced with a much smaller dose. They consider this latter phenomenon as a factor in the relapsing infections as they occur in man. They tested toxin intradermally in humans and obtained strong reactions in those with a history of recent infections and in those with small lesions (boils and sycosis) but severe cases usually gave negative reactions. They also compared this to the allergic phenomena in tuberculosis. Julianelle and Wieghard obtained from staphylococci two type-specific carbohydrates: Type A from virulent pyogenic strains, the other, Type B, from non-pathogenic strains. Two convalescent patients gave skin reactions to 0.1 cc. of a 1 to 50,000 dilution of Type A carbohydrate but not to Type B.

Lethal Toxin. The lethal effects of filtrates are the most dramatic of all toxic manifestations. With strong toxins there is practically no incubation period after intravenous injections and death is very rapid. This toxin is, therefore, different from the other commonly studied toxins such as diphtheria and tetanus and does not seem to be primarily a neurotoxin, although many include parts of the nervous system as affected in its general toxic action. The macroscopic lesions may be few, but if death is delayed for a few hours a serous pericarditis is noted (Nélis *et al.*) or sometimes a peritoneal exudate or hemorrhages in mediastinum, kidney and other organs. The microscopic study indicates a profound destruction of red blood cells in the veins, a lysis of the protoplasm of liver cells and other similar but less regular changes in other parts. These workers believe that death in acute cases is due to cardiac deficiency of sinus origin and in delayed death to functional deficiency in many organs as the liver, kidney and lungs. Antitoxin inhibits these effects. Burky[1] found that one type of coccus (strain Ha) kills in this general way, the other (Fs) kills after producing multiple abscesses. There is scarcely space to consider in further detail this lethal poison, but it should be emphasized that by analogy similar pure toxic deaths are considered as possible in man. If they do occur, it is only on very rare occasions and the human problem is much more often a pyogenic one. Practically all investigators have reported that there is no correlation between the degree of toxin production *in vitro* and the severity of the infection induced in the human by a given strain.

Antitoxin. It is rational to use antitoxin for cases in which the immunology is quite clear and, indeed, antitoxin is being rather widely tested. In animals, although clean-cut results have been obtained in toxin-antitoxin experiments, there is a great deal yet to be learned about its mode of action and the effects of it in humans. Medical history is filled with laboratory experiments which have not fulfilled expectations in the clinic. The protection against injections of living virulent cocci is difficult to obtain. Connor and McKie[2] were only successful in immunizing 3 of 11 rabbits against injections of living cocci by the use of living subcutaneous vaccines followed by toxoid. Parish, O'Meara and Clark have been successful in immunizing rabbits with toxoid against intracutaneous and very occasionally against many

lethal doses of virulent cocci intravenously, but passive immunity against virulent cultures usually only delayed death. Burky[2] found two types of immunity according to the kind of rabbit used: one is an antitoxic immunity, rather permanent, in rabbits not readily growing hair after depilation and produced by his toxic strain (Ha); the other is a kind of desensitization immunity by all filtrates and is only temporary. Winzeler gave living virulent cultures to guinea pigs by dropping in the throat from a syringe, with starvation before and after, and succeeded after 3 to 4 weeks in protecting 17 of 25 against three times the fatal subcutaneous dose.

The results of the use of antitoxin in the human is difficult to evaluate because of the lack of reliable statistics and the very wide variation in the reaction of human beings at different ages and under different conditions to staphylococcus infections. Patients with apparently the most severe kind of infections often recover, so that it is wise to be ultracautious in interpreting results. As an example, the report by Nesbit of 48 cases of acute staphylococcal infections of the kidney apparently of hematogenous origin can bear careful consideration. These patients have a stormy first week followed by a gradual improvement, so that a normal temperature and no pain is the rule by the fourteenth day and without surgical interference. Uncomplicated cases end in complete recovery and none become chronic. He had only 4 (8.3%) with perinephric abscess requiring operation. Even primary staphylococcic pneumonia is not always as fatal as is generally supposed. Reimann lost only 2 of 6 such cases. The blood cultures remained negative in all. Panton, Valentine and Dix, in discussing the difficulties in assessing results after antitoxin treatment, say that in the ordinary case of acute osteomyelitis before exposing the bone blood cultures are positive in about 90% but that this is not prognostically bad. Pyrah and Pain had a mortality rate of 27.1% among 262 consecutive cases of osteomyelitis in which operations were done. Gross considered antitoxic serum should only be used for cases with septicotoxic symptoms, for severe cases of osteomyelitis, carbuncles on face and neck and those where toxin absorption is definitely present. In 1934,[4] he discussed the bases for serum therapy in osteomyelitis, indicating that the defenses here are phagocytic leukocytes and antitoxin. The serum from such cases should be tested for antihemolytic, antinecrotic and antilethal action. He recommends the use of serum from osteomyelitis convalescents with high antitoxin content and if the serum of horses is to be used the strains of Group II staphylococci, with lessened hemolytic and lessened necrotoxic characters should be used for immunizing. Panton, Valentine and Dix treated 13 cases, carefully chosen for their severity, with antiserum containing antileukocidin given intramuscularly in all but 1. The results in 5 cases with severe carbuncles were indefinite, the first 2 were benefited, the last 3 not, but 1 of these was truly hopeless. All 5 cases of septicemia and pyemia recovered, a striking result being obtained in 1 case of osteomyelitis; but there never was a dramatic fall in temperature and pulse rate. Three fulminating cases died. They believed the serum therapy prevented death in some and shortened the course in all. The most extensive use of antitoxic serum is given in a paper by Dolman[3] in which he reported 104 cases so treated. The intravenous route was used in most of the cases "and usually occasioned a severe reaction" with "rigors," sometimes almost "delirium and then circulatory collapse and hyperthermia." Burky,[5] in his study on rab-

bits treated with immune serums, says "certain serums, supposedly immune and with high precipitin titers, seem to increase the lethal action of the toxin." Dolman, because "a number who eventually died . . . lived several days longer than was at first anticipated" and because "a few hours after—some—showed a remarkable improvement," did not seem to be impressed by the probable danger of such reactions on the kidney, heart or other organs. His general results show that 62.5% recovered. All but 2 of these patients were treated in hospital. If we leave out the 24 cutaneous and subcutaneous cases, none of whom died, the recovery rate is 51.25%. The group of 32 cases of staphylococcemia in children secondary to osteomyelitis, which he particularly stresses, showed a recovery rate of nearly 69%, and the balance of 48 cases showed nearly 39.6% recovery. Accepting that children are somewhat less sensitive to staphylococcus infection, that bacteriemia in osteomyelitis cases (see above) may not be prognostically bad, and that in the series of osteomyelitis cases reported by Pyrah and Pain the recovery rate was 72.9%, it would appear that the use of antitoxin serum in the general run of infections is scarcely encouraging. In the group with staphylococcemia, leaving out those secondary to osteomyelitis in children, the recovery rate is about 22%. An annotation on the above report (*Lancet*, **2**, 26, 1934) says that "the striking difference between the mortality in these 'negative (blood) culture' cases (4 deaths among 40) and in the 'positive' (35 among 64) shows that staphylococcal antitoxin cannot be expected to work miracles in face of an established septicæmia with multiple metastatic abscesses." The difficulty in forming a definite estimate of the effect of antitoxin in such pyogenic infections is pointed out and "since no satisfactory controls can be provided, one has to rely mainly on clinical evidence of improvement" which accompanied by an increase in the antitoxin content of the patient's serum occurred in this series and indicated "that antitoxin is of real value." It is clear how extremely hard it is to draw conclusions in this matter. Even in such highly fatal infections as those of the brain and meninges, in which 4 of 6 cases recovered, each case must be considered on its merits. One of the recovered cases of meningitis had received active bacteriophage with no immediate results, but since at least 3 cures of meningitis have been attributed to bacteriophage (for reference see Eaton and Bayne-Jones), and that other immunologic effects besides direct lysis have been suggested in bacteriophage therapy, its bearing on this case cannot be summarily dismissed. The second case of meningitis seems to have been definitely benefited and recovered following intracisternal and intramuscular injections. The third case died. Of the 3 cases of brain abscess, 1 had been treated with toxoid previously and at and after operation with antitoxin and would undoubtedly have recovered but for the erysipelas and the resulting streptococcus meningitis; the other 2 cases recovered after drainage, the antitoxin being used to prevent meningeal involvement. Two other fatal cases secondary to staphylococcemia are also recorded under another heading. Antitoxin has certainly not fulfilled our expectations.

Toxoid. The fact that toxoid preparations could readily be made from staphylococcus toxins has helped greatly in the study of the subject. However, we need not review the details of its production and use in obtaining antitoxin in animals. It is generally agreed that the fundamental antigenic characteristics distinguishing the crude or

purified toxins are more or less retained after formaldehyde treatment. Its use for inducing antitoxin in man is receiving much attention. From what has been said, the limitations of pure antitoxic immunity for the complicated problems of these pyogenic bacteria with their multiple biologic qualities will, we hope, have been made evident. It seems a perfectly logical procedure to build up antitoxin as a defense mechanism if it is reasonably certain that no abnormal or harmful sensitization will later result. The use of vaccines with killed cocci has had a long and variable history of great successes and as many failures. The problem should be restudied with the newer knowledge available and careful comparative and combined results thoroughly analyzed. Barber and Forman tested vaccines intradermally in sycoses, the most difficult of all infections to cure. He obtained 9 complete cures after prolonged treatment with graded increasing doses, 3 almost complete and 1 with the sycosis cured but a blepharitis remaining. These cures were more permanent than by other methods. Connor and McKie[2] treated 18 cases of sycoses—because of the comparative rarity of spontaneous or any cure—with toxoid, with cure in 10 and in 4 with a few pustules still appearing each week in spite of the presence of a high antitoxin in the blood. Nineteen other superficial infections gave equally good results. Dolman[3] successfully treated with a pooled toxoid 28 patients with intractable staphylococcus infections (16 with severe boils, 6 with pustular acne, 1 case each with acute bullous impetigo, recurrent eczema, severe pustular dermatitis, extensive cellulitis after laparotomy and 2 of sinusitis). Antitoxin (antihemolysin?) developed in all and the doses varied from 2 to 20. He concludes that "cases of recurrent and persistent boils, in my experience, invariably respond to toxoid treatment."

Kindel and Costello tested a commercial toxoid made from a potent necrotizing toxin on 42 cases (acne vulgaris, 28; furunculosis, 6; sycosis vulgaris, 8). The acne cases, because due to a combined infection, are not as useful for the purpose as are pure infections. Of the 8 cases of sycosis, 4 were unimproved by the treatment and 4 were worse; of the 6 cases of furunculosis, 3 were improved and 3 were worse. This report, which cautioned against becoming overenthusiastic about the method, resulted in a letter of protest from Dolman,[4] who rightly emphasized certain important features of the toxoid he had used. Cornbleet and Rattner supported the views of Kindel and Costello, having had unsatisfactory results with sycosis barbæ and good results in only 2 of 4 cases of furunculosis, in 1 of which a relapse followed, while 1 man developed a huge carbuncle on the thigh after an "adequate" number of injections of toxoid in the arm. Sharlet suggests that Dolman had not appreciated the toxoid situation in the United States, where the products from manufacturers of biologics are often tested and endorsed under relatively unfavorable conditions. Parish, O'Meara and Clark treated patients with superficial boils and pustular acne with toxoid and say that "a few have ascribed the rapid disappearance of their boils to the injections of toxoid," and all showed an increase in antitoxin titer. Gilchrist and Wilson being impressed with the high incidence in their diabetic patients of staphylococcic infections in the upper respiratory tract, and believing that the staphylococcus toxin increases the metabolic rate and is, therefore, detrimental to the patient, used toxoid with most satisfactory results. The dose of insulin could be reduced and the improvement continued in spite of

adverse weather conditions. It may be of interest that Danbolt, in studying the epidemiology of furunculosis, concluded that the frequent finding of similar types of cocci in the nose and in the furuncles indicated that this nasal infection might play a rôle. Neither bacteriophage nor vaccines had any effect on the nasal staphylococci.

Bacteriophage. The belief that bacteriophage was of marked value in the treatment of staphylococcus infections was shaken when it was shown that blood and tissue fluids inhibited the action of phage. Mutsaars, in 1931, showed that the bacteriophage becomes fixed on staphylococci living or dead and that normal serum prevents this fixation but does not destroy the phage even after a month's contact. He did not find that serum inhibited the action of phage on Staphylococcus albus nor did it affect the absorption. He compares this result with the coagulase action of Staphylococcus aureus and its absence in Staphylococcus albus. d'Herelle and Rakieten claimed that hemolytic staphylococci (tested on rabbit, guinea pig or human blood agar) are particularly susceptible to bacteriophagy and resistant strains are generally of the non-hemolytic type. This has not been the opinion of many and susceptibility does not seem to follow any rule. Every staphylococcus, whatever its other characteristics, must be tested to determine its susceptibility. McKinley calls attention to the fact that at least 39 hemolytic strains have been studied which are resistant to bacteriophagy. Jern, Howes and Meleney found only 8 among their 110 freshly isolated strains were resistant to bacteriophage. They demonstrated that phage instilled into the cutaneous lesions did not increase, but persisted there for a day or more and only gradually became weakened. Although the disappearance of cocci was negligible, there seemed some correlation between this persistence and the apparently marked benefit from the treatment; but there was no correlation between persistence of phage and the presence of so-called "antiphage" in the patients' serum. The changes noted in the cocci after phage treatment were towards loss of virulence which occurred frequently in the test tube but less often in the lesions. Wollman and Wollman studied the secondary lysis of dead staphylococci in the presence of phage and showed that in sealed tubes this occurs only when living susceptible staphylococci are added with the phage, the same phenomenon occurring when resistant living strains of the same type are used in place of the dead cocci. This lysis is not transmissible. There are certain products (diastases ?) set free in the bacteriophagic process which accounts for the action. They suggest this as a method for obtaining lysates of refractory staphylococci. Whether such an occurrence can take place *in vivo* is not discussed. Rakieten reported on this same subject. He found that the lysis of a resistant strain occurs under the action of the bacteriophage lysin when it is in contact with the regenerating phage. He refers to bacteriophages which are not inhibited in whole blood or pure serum, also to strains of non-hemolytic staphylococci which absorb large quantities of some polyvalent bacteriophages and destroy others. The real reason for the inhibiting action of body fluids under artificial conditions he considers as yet unknown. Burky[4] studied the inhibiting action of animal sera and purulent exudates which he confirmed. His type strain of toxic staphylococcus Ha is very resistant to bacteriophage, while strain Fs, a pyogenic type, is sensitive. Immune serum does not inhibit the action of bacteriophage on the Fs type, and this suggested that antitoxin might enhance the effectiveness of

bacteriophage in infections produced by this Fs type (osteomyelitis and other purulent lesions) which in itself produces no toxin and hence no antitoxin can be formed in the patient. He believes the failure of bacteriophage in the tissues is due to the increased resistance of the Ha type. Larkum discussed the suggestion of d'Herelle, that bacteriophage was an antitoxin. Toxin and antitoxin are now well known and he has studied how they are related to bacteriophage. Bacteriophage is not hemolytic for rabbits' red cells; it did not inhibit the hemolytic action of toxin but, injected purified or unpurified into rabbits, it produced sera which were antihemolytic and antinecrotic. He, therefore, concluded that bacteriophage is neither toxin nor antitoxin but is apparently of the nature of a toxoid. The importance of these findings in the therapeutic use of staphylococcus is emphasized in another article. Schultz and Gebhardt, having been successful in curing a series of horses suffering from boils as well as getting benefit in a variety of infections in man by the use of bacteriophage lysates, consider that these are more potent antigens than are vaccines. MacNeal *et al.* bring experimental evidence that the mechanism of bacteriophage action in experimental staphylococcus bacteriemia is the stimulation of endothelial phagocytosis, the restraint of growth of those cocci which have lodged in the internal organs and a favoring action on intracellular digestion. The therapeutic applications of bacteriophage in general have been fully reviewed by Eaton and Bayne-Jones, in which staphylococcus bacteriophage is carefully considered. They emphasize the frequent lack of critical analyses by the advocates of this therapy, but conclude that "staphylococcus infections in general appear to have responded the best to bacteriophage therapy." Bacteriophage cannot therefore be dropped from the list of things to be studied in any real approach to the solution of the problems of staphylococcus infection.

Food Poisoning. A word may be added about a few of the more recent developments in the problems of staphylococcus food poisoning. Only certain species of monkeys, and man irregularly, have been found to be sensitive to the ingestion of the toxic substance. Borthwick, however, has been able to bring about death in the guinea pig and the rabbit, in from 2 minutes to 5 days, by putting the toxin from toxicogenic strains of Staphylococcus aureus (from a carbuncle and also Burnet's strain) into their stomachs after the acid contents had been reduced to a pH value near to 7.3. This observation, if confirmed, may lead to a better explanation of these outbreaks. Dolman[5] was unable to obtain any effects when various filtrates containing potent exotoxin were consumed in milk or water by 42 volunteers on 110 occasions and at various times before and after meals. A filtrate, however, from a strain of the food poisoning type received from Jordan caused severe gastro-intestinal disturbances in 3, and to a lesser degree in 4 of 9 volunteers, and in 1 person after the exotoxin had been fully neutralized with antitoxin. This strain, originally isolated from an abscess in a human, gave white colonies (later becoming pale cream colored) and hemolysis on sheep blood agar. It produced no exotoxin when grown in broth in air after 60 hours nor had it any effect on 5 volunteers who drank it. However, when grown in 0.3% agar in CO_2 it yielded a filtrate giving reactions for both toxic factors, killing a rabbit and producing symptoms in man as recorded. He believed the substance responsible is distinct from the exotoxin, is only produced by an occasional strain

under very special conditions and that the actual incidence of staphylococcic food poisoning is, therefore, not likely to be high. Crabtree and Litterer report a series of severe outbreaks of milk poisoning, with 242 cases among 97 people at a farm school in a period of 50 days. The responsible organism (Staphylococcus aureus) was traced to 2 cows from a herd of 13. It would appear from their study that the staphylococcus had opportunities to grow in the milk stored in large cream cans and under these conditions had produced the poisonous substance, but whether these conditions simulated those postulated as necessary by Dolman is not altogether clear. A more complete study of the toxin of these particular strains will be awaited with interest.

The progress during the last few years has greatly increased the knowledge of the mode of infection and wide potential powers of the staphylococci and there is a hope that more scientific methods of treatment and prevention may develop if all the various aspects of the problem can be properly correlated and effectively evaluated. It is a difficult subject with many aspects not touched upon in this review, such as the influence of diets, trauma, the age incidence and the therapeutic effect of local rest. Such a discussion as Hallam has given on recurrent boils, in which toxin is not mentioned and vaccines are perhaps underestimated, merits reading. He emphasizes that more fatalities come from furunculosis than from any other skin disease.

W. L. Holman.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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EPIDEMIC ENCEPHALITIS.

WITH SPECIAL REFERENCE TO THE ST. LOUIS OUTBREAK OF 1933.

THE occurrence of the first important outbreak of epidemic encephalitis in the United States in St. Louis, Mo., during the summer of 1933, has aroused interest in the study of this disease or group of diseases, depending on whether one considers the various clinical entities as due to one or more than one etiologic agent.

Practically all workers in this field are in general agreement that a virus is the cause of the various clinical conditions encountered. Apparently the only exception is Rosenow, of the Mayo Foundation, who found streptococcus in a goodly proportion of the St. Louis cases, having isolated the organism either from the blood stream or from the upper respiratory passages. Weil found cocci in the central nervous system of fatal cases but, though suggesting that they should not be dismissed lightly, did not express any opinion as to their significance.

Three types are generally recognized, based on clinical, pathologic and epidemiologic grounds: (1) Lethargic encephalitis of von Economo, sometimes spoken of as the "winter" type, or Type A. As one of the synonyms indicates, the onset appears to be more frequent in the winter than in the hot months of the year. (2) The postinfectious type sometimes seen after measles, whooping cough and other infectious diseases, but chiefly studied in recent years as a sequel to vaccinia. (3) The epidemic type, which is regarded as the type that prevailed in St. Louis. This type has prevailed in Japan since approximately 1871. It is usually designated as the B, or Japanese, type. Neal, after studying the St. Louis outbreak, considered it probable that these various types are manifestations of the infection by one virus. Neal later expresses the view that more than one virus is concerned in the causation of acute epidemic encephalitis. Her classification would make two types from the clinical-pathologic point of view: (*a*) Meningoencephalitic type, and (*b*) encephalomyelitic type.

To illustrate the difficulty in classifying these central nervous system manifestations of various diseases it may be noted that Neal regards the Australian outbreak of 1917–18, usually designated as "X" disease, as probably epidemic encephalitis, while Flexner, on the basis of pathologic findings, regards it as more suggestive of poliomyelitis. Possibly, as Neal suggests, both encephalitis and poliomyelitis were present in the outbreak of "X" disease. The clinical symptoms did not fit either in a satisfactory manner.

Rivers is unwilling to express any final opinion on the identity or non-identity of the virus in the different epidemics. He calls attention to the fact that the same neurotropic virus may give very different clinical pictures and refers to a comparatively recent outbreak of rabies in the Island of Trinidad where the clinical picture was that of Landry's paralysis.

Leake, of the Public Health Service, who perhaps devoted more study to the St. Louis epidemic than any other one person, is disposed to regard the virus then prevailing as separate from the one which probably gives rise to the other types of encephalitis.

Webster and Fite, on the basis of serum neutralization tests, indicate that the Japanese B virus is different from the St. Louis virus.

Wooley and Armstrong, from their serum-virus neutralization tests, are disposed to consider the St. Louis virus as an entity different from the virus causing the other types of encephalitis, and practically proved it to be different from the virus of the A type, the virus of postinfectious encephalitis and the virus of poliomyelitis.

Brodie found the serums from cases of chronic encephalitis showing Parkinson syndrome (presumably endemic encephalitis of the von

Economo or A type) devoid of virus neutralizing antibodies for the St. Louis strain.

If anything were needed to complicate the picture of confusion, it is to be found in the fact that Armstrong and Lillie have isolated from one of the St. Louis cases a virus which, in its behavior in animals and production of pathologic appearances, differs from the other viruses isolated in the same outbreak.

Finally, Weil, on the basis of von Economo's studies and his own experience (the latter in the field of pathology), feels that neither clinician nor epidemiologist is in position to decide as to the identity or non-identity of the St. Louis epidemic with other epidemics. Several workers have succeeded in establishing and maintaining strains of the St. Louis virus in monkeys and mice; other laboratory animals appear to be insusceptible.

The clinical features are important in establishing the type of the infection prevailing. The incubation period may be anywhere from a minimum of 4 days to a maximum of 21 days, usually being from 9 to 14 days. The characteristic symptoms as manifested in the St. Louis outbreak were sudden onset, high fever (104° to 105° F.), headache, stiff neck, nausea, disorientation, tremors, abolition of abdominal reflexes. Drowsiness was common, but coma was rare. The leukocyte count was either low, normal or elevated. The spinal fluid was found to be clear in the majority of cases under moderate pressure and carrying cells from 100 to 300, lymphocytes predominating. In 7% of the cases, however, the spinal fluids presented no cellular abnormality. The first spinal fluid may be normal while a subsequent one shows characteristic changes. Spinal fluid sugar, according to Barr, is well above the range seen in tuberculous meningitis. There were few cases, or none, with disturbances of the ocular muscles such as are so common in the von Economo type of the infection.

The Parkinson syndrome, mental changes and other indications of grave disturbance of the central nervous system so common after attacks of endemic encephalitis were conspicuous by their absence after recovery from the St. Louis type. From the clinical point of view, the relative absence of sequelæ is perhaps the most striking difference between what we would prefer to call the epidemic type of encephalitis and the endemic type (von Economo or A type).

McFadden, on the other hand, found a few evidences of residual nerve system damage in some patients at the time of discharge from the hospital and suggests that time may show serious sequelæ.

The death rate was approximately 20%, but when recovery occurred it was prompt. Kinsella and Broun say the average patient was well in 10 days, but they also note that minor disabilities were not unusual. They agree with other observers, however, that the serious sequelæ so common after the lethargic type did not follow attacks of the St. Louis type of the disease.

Most observers note that there were mild cases, cases which surely would not have been recognized in the absence of an epidemic.

Eschenbrenner reports that no special therapeutic agent appeared to be of value in treatment; even convalescent serum appeared to be of little value; Finnigan thought antistreptococcus serum of value. Neal urges that hospitals especially designed for encephalitis patients should

be provided in the interest of patients, their families and the furthering of treatment and research.

The epidemiologic features of the outbreak were of special interest. There was a total of over 1000 cases reported. The earliest came from the suburban areas of St. Louis early in the month of July, and it was not until the end of that month that cases began to be recognized in the city proper. Retrospective diagnoses then and later indicated that some cases even earlier had been missed. The epidemic had a direct seasonal prevalence, being confined to the hot part of the year. This agrees with the experience in Japan where hot, dry seasons are prone to be associated with outbreaks of the disease. An interesting feature was the fact that not only did the outbreak appear to begin in the rural areas but also the highest incidence was not in the crowded part of the city but in the much less densely populated surrounding country. Race and sex appeared to offer no significant differences in incidence. The older age groups (above 35) show a higher attack rate than the younger. Multiple cases in families were very unusual, indicating that the infection is not readily communicable.

The exact mode of spread remains to be determined. It has been customary to say that it was similar to the spread of poliomyelitis, but this, in reality, is not advancing one's acquaintance with the subject very extensively. It is interesting to note that cases originating from infection in St. Louis, which developed the disease elsewhere, did not result in any material spread of the disease in other communities though a few neighboring cities had a modest number of cases; whether or not these originated from cases infected in St. Louis could not be determined.

Early in the epidemic, mosquitoes came under suspicion as possible vectors but these, together with food and water, were excluded. Studies by Wooley and Armstrong on the distribution of the virus of endemic encephalitis in the United States indicate that, on the basis of serum-virus neutralization tests, the infecting agent appears to be much more widely distributed than had been suspected. They found that serum of about 95% of recovered cases neutralized virus while serum from 35.7% of contacts of clinical cases neutralized the virus, and 9.4% of normal non-exposed persons yielded serum which gave neutralization. Geographically, they found a very wide distribution of individuals whose serum would neutralize the St. Louis virus. This finding raises the question as to why epidemics are so rare when the virus appears to be so widely distributed.

With respect to control measures, it is obvious that little can be said in view of our lack of knowledge of the means of transmission. It was customary in St. Louis to hospitalize patients as far as possible for two reasons: (1) To effect isolation, and (2) for better opportunity for early diagnosis. This isolation was maintained for 3 weeks from onset. Schools were kept open. Bredeck, Commissioner of Health, St. Louis, whose opinion is entitled to the greatest weight, has the following to say with respect to the public health aspects of the disease:

"That the measures of early diagnosis, hospitalization and isolation were efficient can be measured only by the fact that 95% of the reported cases were hospitalized. How successful in checking the disease this was is a matter of speculation. There is no actual method that we

can apply in determining the efficiency of such measures. They are, however, those that have been recognized in the handling of all communicable diseases. Our greatest consolation was in the fact that we did not issue regulations which were not based on sound public health practice. Until more fundamental knowledge is forthcoming concerning the true etiology, mode of spread, or specific remedies for this disease nothing could be advocated further."

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 21, 1935.

The Excretion of Reducing Materials in the Urine of the Normal Dog. EDWIN P. LAUG (Laboratories of Physiology, University of Tennessee and University of Pennsylvania). The estimation of carbohydrates in bread by *in vitro* and *in vivo* (phlorhizin) methods reveals only their gross availability, without distinguishing more subtle modifications resulting from heat treatment. By using a sensitive method for detecting reducing materials in specially prepared urine filtrates, the hourly changes in non-fermentable, fermentable and hydrolyzable fractions in the urine of 2 normal dogs was studied. Feeding various kinds of bread preparations resulted in the following observations:

1. Crust, in contrast to white inside portions of bread, caused a considerable rise in total reducing materials; of this rise, 92% was accounted for by the increase in the non-fermentable fraction.

2. After three different kinds of bread, the response in excretion of reducing materials was lowest with rye, intermediate with wheat an highest with whole-wheat bread.

3. The reducing material revealed by hydrolysis of urine filtrates

was practically 100% fermentable and was not produced at the expense of the non-fermentable material present before hydrolysis. After whole-wheat feeding, however, the hydrolyzable fraction decreased by about 50% and was only 25% fermentable.

Histamin and Leukocytosis. V. H. Moon (Laboratory of Pathology, Jefferson Medical College). The discovery of histamin in the various tissues of mammalian animals has led to intensive investigation in attempts to discover its physiologic significance. It appears that histamin performs several functions, some of which are important factors in the inflammatory reaction. Apparently the effect of histamin upon leukocytes in the circulating blood has not been thoroughly studied. Perhaps this is due to an early incidental observation to the effect that histamin produces leukopenia. Attempts to verify this observation have led to results of the opposite character. The intravenous injection of histamin phosphate, in doses ranging from 1 to 2 mg., into cats was followed regularly by leukocytosis. The increase in leukocytes was evident within 15 minutes and continued to a maximum 2 hours following the injury. The leukocyte count remained high for 6 to 8 hours and subsided approximately to normal in 24 hours. Similar results followed the subcutaneous injection of histamin phosphate in monkeys. The increase was chiefly among the polymorphonuclear leukocytes. Injections of saline solution under the same experimental conditions were not followed by significant changes in the leukocytic counts. Differential counts made on cats resulted in the following average leukocytic formula:

Polymorphonuclear leukocytes: Normal, 47; after histamin, 68.
Lymphocytes: Normal, 50; after histamin, 30.
Monocytes: Normal, 3; after histamin, 2.

A Comparative Study of the Actions of Morphin and Dilaudid (Dihydromorphinone Hydrochlorid) on the Intact Small Intestine of the Dog. Charles M. Gruber and John T. Brundage with the occasional assistance of Anthony DeNote and Raymond Heiligman (Laboratory of Pharmacology, Jefferson Medical College). Intestinal activity as influenced by morphin and dilaudid was studied in unanesthetized dogs with Thiry-Vella loops of the jejunum and ileum, using balloons, 30 to 70 mm. long, 20 mm. diameter under a pressure of 15 cm. of water. The drugs were dissolved in Ringer's solution and injected intravenously. The minimal dose of dilaudid causing an increase in general tonus was found to be 0.0002 and 0.0003 mg. per kg., respectively, for the jejunal and ileal loops. The corresponding amounts of morphin were 0.002 and 0.003 mg. per kg. In small and medium doses, dilaudid is ten times more active than morphin in causing an increase in general tonus. Large doses of dilaudid cause a decrease in general tonus of the jejunum and cause less increase in the general tonus of the ileum than do medium doses.

The average rate of the rhythmic contractions of the ileum in the unanesthetized dog is 10.8 contractions per minute, and for the jejunum 13.3 per minute. The effects of morphin and dilaudid upon the rate of the rhythmic contractions are not constant and no conclusions could be drawn.

The effects of these drugs upon the peristaltic activity are also variable; sometimes they cause a disappearance of these movements and at other times these drugs increase their amplitude and rate.

The Permeability of Living Cells to Heavy Water (Deuterium Oxid). BALDUIN LUCKÉ (Laboratory of Pathology, University of Pennsylvania). The unfertilized egg of the sea urchin, Arbacia punctulata, has been used as a cell which allows accurate determination of permeability to water and ready recognition of injury.

It was found that the rate of penetration of heavy water, D_2O, is the same as that of ordinary water, H_2O. The physical differences between these two fluids are, therefore, not of sufficient magnitude to effect differences in their rate of cell penetration under the driving force of osmotic pressure.

As has been reported for most other biologic material tested, D_2O in sufficiently high concentration proved injurious to the test cell. This was indicated by inhibition of development of fertilized cells. However, the similarity in rates of penetration of D_2O and H_2O observed in the present experiments may be regarded as evidence that heavy water does not exert its injurious effects through (rapid) changes in cell permeability.

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